Diffusion-weighted imaging lesions and risk of recurrent stroke after intracerebral haemorrhage

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Abstract

Objective: To determine whether the presence of DWI+ lesions is associated with recurrent stroke after ICH.

Methods: The REstart or STop Antithrombotics Randomised Trial (RESTART) assessed the effect of restarting versus avoiding antiplatelet therapy after ICH on major vascular events for up to 5 years. We rated DWI sequences of MRI done before randomisation for DWI+ lesion presence, masked to outcome and antiplatelet use. Cox proportional hazards regression models were used for statistical analysis. The trial is registered with the ISRCTN registry, number ISRCTN71907627.

Results: Of 537 participants in RESTART, 247 (median [IQR] age 75.7 [69.6-81.1] years; 170 men [68.8%]; 120 started vs. 127 avoided antiplatelet therapy) had DWI sequences on brain MRI at a median of 57 days (IQR 19-103) after ICH, of whom 73 (30%) had one or more DWI+ lesion. During a median follow-up of 2.0 years (1.0-3.0), 18 participants had recurrent ICH and 21 ischaemic stroke. DWI+ lesion presence was associated with all stroke, (adjusted hazard ratio [HR] 2.2 [95% CI 1.1-4.2]) and recurrent ICH (4.8 [1.8-13.2]), but not ischaemic stroke (0.9 [0.3-2.5]). DWI+ lesion presence (0.5 [0.2-1.3]) versus absence (0.6 [0.3-1.5], $P_{interaction}$=0.66) did not modify the effect of antiplatelet therapy on a composite outcome of recurrent stroke.

Conclusions: DWI+ lesion presence in ICH survivors is associated with recurrent ICH, but not with ischaemic stroke. We found no evidence of modification of effects of antiplatelet therapy on recurrent stroke after ICH by DWI+ lesion presence. These findings provide a new perspective on the significance of DWI+ lesions, which may be markers of microvascular occlusive events that are associated with recurrent ICH.

Introduction

Worldwide roughly ~3 million people suffer spontaneous intracerebral haemorrhage (ICH) every year.[1] In most patients, ICH results from cerebral small vessel disease (SVD), affecting the small perforating vessels of the brain. Survivors of ICH are at high risk for recurrent stroke (both recurrent ICH and ischaemic stroke) and other vascular events.[2, 3]

Diffusion-weighted imaging-positive (DWI+) lesions are present in 11-41% of patients on brain MRI performed days to months after ICH.[4-14] A recent meta-analysis investigating the association between DWI+ lesions and various subtypes of ICH showed that the prevalence of DWI+ lesions within 90 days after ICH averages 20%.[15] Furthermore, in all ICH, DWI+ lesions were associated with previous ICH and with other SVD biomarkers on brain MRI.[15]

Whether DWI+ lesions predict clinical events after ICH is still uncertain. Poor functional outcome (assessed by the modified Rankin Scale [mRS] score at 3 months after ICH) was associated with the presence of DWI+ lesions in some studies,[6, 16, 17] but not others.[9, 13] One study of 97 patients found that the presence of DWI+ lesion(s) five days after ICH was associated with a higher risk of both ischaemic stroke as well as a composite of ischaemic stroke, recurrent ICH, and vascular death, during a median follow-up period of 3.5 years.[9] However, another study of 466 patients with ICH found that presence of a DWI+ lesion was associated with a higher risk of ischaemic stroke, but not recurrent ICH.[3]. Therefore, we aimed to investigate whether DWI+ lesion presence in antithrombotic-associated ICH survivors was associated with recurrent stroke, in a post-hoc exploratory sub-group analysis of RESTART.

Methods

Study design and participants

RESTART was a prospective, multicentre, randomised controlled trial in 122 hospitals in the United Kingdom, which aimed to estimate the effect of restarting versus avoiding antiplatelet therapy on the risk of recurrent ICH, and whether this risk might exceed the expected decrease in the number of vaso-occlusive events by antiplatelet therapy. The procedures and main results of the trial have been described in detail previously.[18-20]

Briefly, we included patients ≥ 18 years old, who were taking antithrombotic (antiplatelet or anticoagulant) therapy until ICH for the prevention of vaso-occlusive disease, and survived at least 24 hours. Antithrombotic therapy had to be discontinued at the time of the ICH, and both the participant and their physician had to be uncertain about whether to start or avoid antiplatelet therapy, meaning that if either one had strong beliefs about avoiding or restarting antiplatelet therapy then the participant was not eligible for the trial. In addition, spontaneous ICH had to be confirmed on brain imaging (computed tomography [CT] or MRI) and made available to the trial-coordinating centre. Participants were excluded if the ICH was due to trauma, haemorrhagic transformation of ischaemic stroke, or if it was not located in the brain parenchyma.

Participants were randomised within 24 hours to start or avoid antiplatelet therapy by a digital minimisation algorithm, which minimised differences between participants in the two trial arms based on five variables: (1) age at randomisation (<70 years vs ≥70 years); (2) ICH location (lobar vs non-lobar); (3) time since symptom

onset (1-6 days, 7-30 days, >30 days); (4) type of antiplatelet therapy if assigned to restart (aspirin vs other); and (5) probability of being alive and independent at 6 months (<0.15 vs ≥0.15).[21]

Standard protocol approvals, registrations, and patient consents

RESTART was approved by the Scotland A Research Ethics Committee and informed consent was obtained from every participant (or their legal representative), including for brain MRI if this had not already been performed. The trial is registered with the ISRCTN registry, number ISRCTN71907627.

MRI acquisition and assessment of brain characteristics

Participants underwent brain MRI at a median of two days before randomisation compatible with the RESTART standardised protocol (http://www.restarttrial.org/documents/RESTART_MRI_protocol.pdf), including axial gradient-recalled echo (GRE) T2*, fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI) including apparent diffusion coefficient (ADC) maps , T2-weighted and T1-weighted sequences (online supplementary table e-1).[19]

As described previously, anonymised images were reviewed in DICOM format by a panel of neuroradiologists blinded to treatment allocation and clinical outcome using the in-house, web-based, Systematic Image Review System (SIRS2) tool (https://sirs2.ccbs.ed.ac.uk/sirs2).[19] In short, this included the rating of ICH characteristics (side, location) on MRI and volume in mL (measured by the ABC/2 method) on CT.[22] Additionally, the following MRI biomarkers of SVD according to the universally standardised STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria,[23] were assessed using validated scales: white matter hyperintensities (WMH);[24] old ischaemic lesions;[23] cerebral microbleeds (CMB); [25, 26] any cortical superficial siderosis, (focal and disseminated),[27] and the probability of cerebral amyloid angiopathy (CAA) according to the Modified Boston criteria.[27]

Diffusion-weighted imaging-positive lesions

We defined DWI+ lesions as hyperintense lesions on diffusion-weighted imaging, that were not located within or immediately adjacent to the haematoma. Presence, number, and location of DWI+ lesions were assessed in Carestream Vue PACS version 11.3.2, Carestream Health, Inc, USA, by one trained rater (KW) blinded to clinical outcome and treatment allocation. DWI and ADC signals change at different rates in white matter versus grey matter, and prolonged DWI-positive signal may indicate ongoing tissue pathological changes instead of T2 shine through.[28, 29] Therefore, acuity of DWI+ lesions was determined based on the corresponding intensity of ADC maps at the location of the DWI+ lesion, and deemed to be in the acute (hypo- or isointense) or subacute (hyperintense) phase. We determined inter-rater reliability of presence or absence of definite DWI+ lesions with one member of the panel of neuroradiologists (PMW) in a smaller subsample (N=40) which indicated substantial agreement (Cohen's kappa 0.73 (95% confidence interval [CI] = 0.51-0.94). The size of a DWI+ lesion was defined as the greatest diameter of the DWI lesion.

Clinical outcomes

We collected follow-up data after randomisation until death or November 30, 2018, as described previously.[18]

Each participant (or their representative) and their primary care practitioner were asked about the occurrence of any serious vascular event, hospital admission, vital status, and medication use. In this study, we focused on recurrent stroke, including symptomatic ICH as evidenced by neuroimaging or pathology,[20] and ischaemic stroke as clinical outcomes. All stroke outcome events were assessed and verified by a neurologist outcome adjudicator masked to treatment allocation according to standardized definitions.[18]

Statistical analysis

KW performed statistical analyses in R (v3.6.2; https://www.R-project.org). We compared baseline demographics, ICH characteristics, and MRI biomarkers of SVD between participants with and without any DWI+ lesions using nonparametric tests. We used the Mann-Whitney test for continuous and chi-square test for categorical dependent variables (or Fisher's exact test where appropriate). We estimated the survival function of time to first occurrence of recurrent stroke, censored at death or final follow-up using Kaplan-Meier survival analysis. We quantified annual event rates with 95% CI. After confirming the proportional hazards assumption with Schoenfeld residuals, we used observational Cox proportional hazards regression models to assess whether DWI+ lesion presence was associated with recurrent stroke (recurrent ICH, ischaemic stroke, or both). As different types of stroke present with different risk factors for stroke recurrence, we used three models including different covariates. Collinearity of covariates in multivariable regression models was analysed using Belsley collinearity diagnostics (mctest R package).[30] The model for ICH was adjusted for age at randomisation, lobar ICH location, probable CAA, and use of antiplatelet therapy (as predictors of recurrent ICH), whereas the model for ischaemic stroke was adjusted for age at randomisation, use of antiplatelet therapy, and atrial fibrillation (as predictors of ischaemic stroke). The model for all stroke was adjusted for all variables included in the other two models. In additional Cox regression models presented in our online data supplement, we replaced probable CAA with the presence of cortical superficial siderosis, since this is a well-known risk factor for ICH recurrence,[31, 32] and investigated the association between DWI+ lesion presence and recurrent stroke stratified according to the qualifying ICH location (lobar vs. non-lobar). Furthermore, we performed two sensitivity analyses. First, we constructed Cox regression models using the sub-distribution hazard method of Fine and Gray to assess the effect of the competing risk of death.[33] Second, we reanalysed these Cox regression models after excluding participants with presence of one or more DWI+ lesion that had no ADC sequence available or who exclusively had subacute DWI+ lesion(s).

We included an interaction term between presence of any DWI+ lesions and treatment group to investigate whether DWI+ lesion presence modified the effect of antiplatelet therapy on recurrent stroke (recurrent ICH alone, ischaemic stroke alone, or any stroke). Cox proportional hazards interaction models were adjusted for the five covariates in the minimization algorithm. Additionally, we repeated these interaction models after excluding individuals without ADC sequences or exclusively subacute DWI+ lesion(s).

Results are presented as hazard ratios (HRs) with 95% confidence intervals (CI). The two-tailed significance level α was set at 0.05.

Data availability

An anonymised version of the RESTART dataset will be available from 22 May 2020 (one year after publication

of the primary findings), upon request to the members of the RESTART trial steering committee by using the online data request form (https://datashare.ed.ac.uk/handle/10283/3632).

Results

537 participants were included in RESTART between May 22, 2013 and May 31, 2018,[18] of whom we excluded 12 from these analyses because they did not have ICH (Figure 1). Of the remaining 525 participants, 254 participants had brain MRI performed according to the RESTART imaging protocol and were included in the brain MRI sub-study.[19] Of the 525 participants, 507 had undergone brain CT; we did not find any differences in demographics, ICH characteristics, and brain CT biomarkers of SVD between the 240 participants who underwent brain MRI and 267 participants without brain MRI (see online supplementary table e-2). Of all 254 participants who had brain MRI, we excluded seven participants with inadequate DWI sequence quality from our analyses. This resulted in a final sample size of 247 participants (median [IQR] age 75.7 [69.6-81.1] years; 170 men [68.8%]) with a median interval between the qualifying ICH and brain MRI of 57 days (IQR 19-103), of whom 120 were assigned to restart antiplatelet therapy, 127 were assigned to avoid antiplatelet therapy, and none withdrew from follow-up.

Among the 247 participants, 73 (30%) had at least one DWI+ lesion. We found a total of 150 DWI+ lesions, with a median diameter of 4 mm (IQR 3-6). DWI+ lesions were located in the cerebral white matter (n=70), cerebral cortex (n=52), cortical grey-white matter junction (n=12), subcortical grey matter (n=7) and cerebellum (n=9). Seventy-seven DWI+ lesions were in the hemisphere contralateral to the ICH (51%) and 73 in the ipsilateral hemisphere (49%). Sixty-four of the 73 participants with DWI+ lesions also had ADC maps available. These 64 individuals had 138 DWI+ lesions, of which 115 (83%) were deemed to be in the acute phase and 23 (17%) were deemed to be in the subacute phase.

The baseline demographic and ICH characteristics of participants with and without any DWI+ lesions did not differ (Table 1). Participants with one or more DWI+ lesion had more severe WMH (Fazekas score 3-6: 77% vs. 63%, P=.039), and higher frequencies of any cortical superficial siderosis (33% vs. 21%, P=.042), compared with individuals without any lesions. There was no difference in the number of participants with two or more CMB (49% vs. 35%, P=.058), more than one old ischaemic lesion 32% vs. 23%, P=.202), or the number of participants with probable CAA (29% vs. 18%, P=.070) according to the modified Boston criteria.

The median follow-up of all 247 participants was 2.0 years (IQR 1.0-3.0). During this period, 18 participants had recurrent ICH and 21 had ischaemic stroke. There was no evidence of a violation of the proportional hazards assumptions of analyses involving recurrent stroke at follow-up or collinearity among covariates in any of the regression analyses. We found a higher risk of all stroke for DWI+ lesion presence versus absence (adjusted HR 2.15 [95% CI 1.10-4.18], P=.025; Table 2; Figure 2; online supplementary table e-3). Participants with at least one DWI+ lesion had a higher risk of recurrent ICH (adjusted HR 4.83 [95% CI 1.77-13.17], P=.002, even when including the presence of cortical superficial siderosis as a confounder (online supplementary table e-4). However, DWI+ lesion presence was not significantly associated with future ischaemic stroke (adjusted HR 0.89

[95% CI 0.32-2.50], P=0.824). The association between DWI+ lesion presence and recurrent stroke remained similar when stratifying analysis according to the location of the qualifying ICH (online supplementary table e-8), except for the association with all stroke after non-lobar ICH. Results were similar using the sub-distribution hazard method of Fine and Gray to assess the effect of the competing risk of death (online supplementary table e-5). Results were unchanged in sensitivity analyses excluding individuals with one or more DWI+ lesion and no ADC map or exclusively subacute DWI+ lesion(s) (n=15; see online supplementary tables e-6 and e-7).

There was no evidence of heterogeneity of the effects of antiplatelet therapy by DWI+ lesion presence versus absence on the risk of any recurrent stroke (adjusted HR 0.45 [95% CI 0.16–1.26] vs 0.61 [0.26–1.47]; $P_{interaction}$=.661; online supplementary tables e-9 and e-10; online supplementary Figure e-1), recurrent ICH (adjusted HR 0.57 [95% CI 0.17–1.87] vs 0.24 [0.03–2.10]; $P_{interaction}$=.499), or ischaemic stroke (adjusted HR 0.26 [95% CI 0.03–2.36] vs 0.82 [0.30–2.21]; $P_{interaction}$=.356). Results were unchanged in sensitivity analyses excluding individuals with one or more DWI+ lesion and no ADC map, or exclusively subacute DWI+ lesion(s) (online supplementary tables e-11 and e-12).

Discussion

We found that DWI+ lesions occurred in 30% of ICH survivors who had been taking an antithrombotic drug before ICH. The presence of one or more DWI+ lesion was associated with recurrent ICH, but not ischaemic stroke.

We found DWI+ lesions in almost one third of our participants; this prevalence is higher than found in a recent systematic review, possibly because of the burden of SVD or prevalence of vascular risk factors in the RESTART population. In the acute phase, ICH might trigger changes in cerebral hemodynamics, blood-brain barrier permeability, induce inflammatory responses, or a decrease in blood pressure, contributing to development of DWI+ lesions. Conversely, acute ICH may reflect an active ongoing process in the small vessels that likely predates the ICH, which could result in the occurrence of DWI+ lesions outside this acute time window. The high prevalence of DWI+ lesions after ICH, the higher burden of MRI biomarkers of SVD in patients with any DWI+ lesions, together with the association of DWI+ lesion presence with recurrent ICH but not ischaemic stroke, suggests that the DWI+ lesions are markers of microvascular occlusive events predisposing to rupture of microvessels. Future research needs to determine whether DWI+ lesions in ICH survivors are a consequence or marker of the underlying SVD, or mechanisms induced by the rupture of whole blood into the brain parenchyma, or both.

The appearance of DWI+ lesions in individuals with acute ICH has been associated with a high risk of either ischaemic stroke or a composite of ischaemic stroke, recurrent ICH, or vascular death in a small study,[9] and with an increased risk of ischaemic stroke, but not recurrent ICH, in a recent pooled individual patient data analysis including 466 patients from the ATTACH-2 and the MISTIE-III trials.[3] In the RESTART MRI sub-study, presence of any DWI+ lesion was not associated with ischaemic stroke; in the small study,[9] four of the five

ischaemic strokes were due to SVD, but we did not investigate the likely cause of the ischaemic strokes we observed during follow-up. Furthermore, the majority of the patients in previous studies had non-lobar ICH associated with hypertension, and very few patients had cortical superficial siderosis, an independent predictor of recurrent ICH. In RESTART, the association between DWI+ lesion presence and recurrent ICH might have been confounded by a slight, non-significant excess of CAA-related ICH in participants with one or more DWI+ lesion (Table 1) even though we adjusted for modified Boston criteria for probable CAA and the association between one or more DWI + lesion and recurrent ICH remained (Table 2). Although the association between DWI+ lesion presence and recurrent ICH did not differ according to ICH location (see online supplemental table e8), DWI+ lesion location might be a marker of CAA-related ICH, so larger studies could investigate whether a cortical DWI+ lesion distribution is associated with an increased risk of lobar ICH.

We did not find any evidence that DWI+ lesion presence modifies the risk of recurrent stroke with antiplatelet therapy. Although the direction of effects in all subgroups was consistent with the main finding of RESTART – that starting antiplatelet therapy may reduce the risk of recurrent ICH when compared with avoiding antiplatelet therapy[18] – the number of outcomes was too small to detect any significant differences between subgroups, and thus needs to be interpreted with caution. Nonetheless, these findings can be informative for sub-group analyses in MRI sub-studies in definitive main phase RCTs and meta-analyses of antiplatelet and anticoagulant RCTs after ICH (see online supplemental table e-13 for a list of the many trials' NCT entries).

The main strengths and limitations of RESTART and the MRI sub-study are described elsewhere.[18, 19] Our findings provide a new perspective on the clinical significance of DWI+ lesions, which may be markers of SVD activity rather than just ischaemia. Other strengths include the multi-centre prospective study design, standardized imaging protocol, blinded expert review of MRI imaging according to widely established criteria, and outcome assessment using standardised definitions.

However, this study has some limitations. First, our findings might not be generalizable to a broader population of individuals with ICH. RESTART participants were already taking antithrombotic agents for the prevention of vaso-occlusive disease before ICH, which tended to be smaller in (median 4.6 mL) compared with ICH volumes reported in the majority of previous MRI-based studies,[7, 8, 12] or population-based cohorts.[34] More severe ICHs are often fatal, and therefore less likely to be investigated by MRI, which may have resulted in an underestimation of the true prevalence of DWI+ lesions. However, we did not find evidence of any selection biases when comparing participants included or not included in the MRI sub-study (see online supplementary table e-2). Second, the prevalence of DWI+ lesions might have been further underestimated due to the broad interval between the qualifying ICH and brain MRI, since prior reports suggest that the early post-ICH period is a high risk time for DWI+ lesion occurrence.[5] Third, the higher prevalences of superficial siderosis in participants with DWI+ lesion presence may suggest an overrepresentation of CAA-related ICH, which could have confounded the association between DWI+ lesions and recurrent ICH,[27] but this association was independent of probable CAA in a multivariable analysis. Fourth, although we made use of a standardized imaging protocol, field strength and parameters of the DWI sequence varied between participants, by which prevalence of DWI+ lesions is likely to be influenced. Fifth, we did not systematically perform brain MRI at a

set interval after ICH, which may have influenced the number of observed DWI+ lesions.[6, 11, 12] Finally, the modest sample size of RESTART resulted in a small number of clinical outcomes, which limited the statistical power to detect any significant effects.

In conclusion, we found that DWI+ lesion presence in survivors of ICH enrolled in the RESTART trial was associated with recurrent ICH, but not with ischaemic stroke. These findings provide a new perspective on the significance of DWI+ lesions, which may be markers of microvascular occlusive events that are associated with recurrent ICH.

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Table 1. **Group characteristics**

	No diffusion-weighted imaging-positive lesions (n = 174)	**One or more diffusion-weighted imaging-positive lesion (n = 73)**	**P**
Demographic characteristics			
Age (years)	75 (68 – 81)	77 (72 – 82)	.121
Men	116 (67%)	54 (74%)	.258

Time between ICH and MRI (days)	56 (19 – 102)	63 (20 – 103)	.753
Characteristics of the largest ICH			
Side			.104
Left	84 (48%)	27 (37%)	
Right	90 (52%)	46 (63%)	
Location of the ICH			.553
Lobar	71 (41%)	35 (48%)	
Deep	84 (48%)	30 (41%)	
Infratentorial	19 (11%)	8 (11%)	
ICH volume (mL) †	5.4 (1.6-13.9)	3.2 (0.9-12.4)	.235
MRI markers of SVD			
Fazekas score			**.039**
0-2	64 (37%)	17 (23%)	
3-6	110 (63%)	56 (77%)	
Old ischaemic lesions			.202
None	107 (61%)	36 (49%)	
One	27 (16%)	14 (19%)	
More than one	40 (23%)	23 (32%)	
Cerebral microbleeds			.058
0-1	105 (65%)	35 (51%)	
2 or more	57 (35%)	33 (49%)	
Cortical superficial siderosis			**.042**
Focal or disseminated	36 (21%)	24 (33%)	
None	138 (79%)	49 (67%)	
Modified Boston Criteria of CAA[27]			.070
Probable CAA	32 (18%)	21 (29%)	
Other	142 (82%)	52 (71%)	

Note: Demographics, ICH characteristics, and biomarkers of SVD of participants with any DWI+ lesions compared to those without were assessed using the Mann-Whitney test for continuous and chi-square test for categorical dependent variables (or Fisher's exact test where appropriate). Data represent median (IQR) or No. (%). Abbreviations: ICH, intracerebral hemorrhage; SVD, small vessel disease; CAA, cerebral amyloid angiopathy. † measured by the ABC/2 method on CT.

Table 2. **Risk of recurrent stroke during follow-up according to diffusion-weighted imaging-positive lesion presence**

	Events/participant (%)		Unadjusted analysis		Adjusted analysis	
	DWI+ (n=73)	**DWI- (n=174)**	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
All stroke	17 (23%)	22 (13%)	2.28 (1.21-4.30)	.011	2.15 (1.10-4.18)	.025
Intracerebral hemorrhage	12 (16%)	6 (3%)	5.36 (2.01-14.28)	<.001	4.83 (1.77-13.17)	.002
Ischaemic stroke	5 (7%)	16 (9%)	0.90 (0.33-2.50)	.858	0.89 (0.32-2.50)	.824

Note: The adjusted model for all stroke includes age, lobar ICH location, probable CAA, antiplatelet use, and atrial fibrillation; the model for intracerebral hemorrhage includes age, lobar ICH location, probable CAA, and antiplatelet use; and the model for ischaemic stroke includes age, antiplatelet use, and atrial fibrillation.
Abbreviations: DWI+, at least one diffusion-weighted imaging lesion; HR, hazard ratio, CAA, cerebral amyloid angiopathy.

Figure 1. **Flowchart of patients with suitable brain MRI studies in RESTART**

Abbreviations: ICH, intracerebral haemorrhage; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging.

Figure 2. **Cumulative proportion of RESTART participants with a first recurrent stroke during follow-up stratified by DWI+ lesion presence vs. absence before randomisation**

Numbers at risk include survivors under follow-up at the start of each year according to presence or absence of diffusion-weighted imaging lesions. Number of cumulative events show the participants under follow-up with a first stroke event. Abbreviations: DWI+, at least one diffusion-weighted imaging lesion; DWI-, no diffusion-weighted imaging lesion.