Brain MRI to personalise atrial fibrillation therapy: current evidence and perspectives

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ABSTRACT

Advances in the access to and in the performance of brain MRI have led to an increased detection of asymptomatic abnormalities in the brain of patients with cardiovascular diseases. These may have prognostic impact and could influence management in the future. In this review, we summarise the main findings of brain MRI in patients with atrial fibrillation (AF) and explore the available evidence to better quantify the risk for intracerebral haemorrhage and (recurrent) ischaemic stroke based on brain MRI findings. Treatment decisions in the majority of patients with AF should still be based on data from established validated risk scores and large randomised trials. Whether brain MRI has the potential to improve the personalised management of patients with AF by guiding the risk and benefit assessment of stroke prevention by oral anticoagulants remains to be established in large prospective studies using standardised brain MRI. However, even today, brain MRI may help to identify subsets of patients with AF at increased risk for (recurrent) intracerebral bleeding. Although present knowledge and MRI-associated costs do not support routine use of brain MRI in asymptomatic patients with AF, as more data emerge MRI may become an increasingly useful way to stratify patients with AF and individualise their treatment.

INTRODUCTION

Atrial fibrillation (AF) is a strong risk factor for ischaemic stroke; moreover, AF-related strokes tend to be more severe compared with non-AF-related strokes.[1] While anticoagulation is highly effective at reducing the risk of ischaemic stroke and death in patients with AF with additional risk factors for stroke, the fear of anticoagulation-related bleeding is a key cause of the underuse of oral anticoagulants in daily clinical practice.[2–4] Unfortunately, similar common cardiovascular risk factors increase both ischaemic stroke and intracerebral bleeding risk in AF, as illustrated by the overlap between clinical risk scores for these outcomes, for example, the CHA_2DS_2-VASc and HAS-BLED.[5] In addition, of the common bleeding risk scores (HAS-BLED, $HEMORR_2HAGES$, ATRIA) developed to predict all types of major bleeding only HAS-BLED has demonstrated a significant predictive performance for intracranial haemorrhage in patients with and without AF.[6] Finding additional ways to identify patients with AF at very high risk for intracranial bleeding or ischaemic stroke may help to individualise treatment decisions on anticoagulation by better balancing the risks and benefits of vitamin K antagonists, direct thrombin antagonists or factor Xa antagonists.

MRI of the brain has the unique potential to provide information about existing cerebrovascular disease that may be highly relevant to future intracerebral haemorrhage (ICH) or ischaemia, even in neurologically asymptomatic patients with AF. Unfortunately, brain MRI is only routinely performed when a stroke is suspected, limiting the information available to assess the usefulness of brain MRI to improve management in patients with AF.

Whether readily available but expensive brain imaging with MRI is able to better personalise the management of AF was recently discussed at the 4th AFNET/EHRA consensus conference, the conclusion being that present knowledge does not support the unselected use of baseline or serial MRI to guide stroke prevention in patients with AF.[7] By contrast, a recent review has already suggested potential clinical value for an MRI-based algorithm for decision making regarding anticoagulation in AF. In this review, we suggest that the evidence supporting the routine use of MRI for risk stratification in AF is not sufficient at present.[8] Indeed, despite the obvious interest in this field, there are only a few published studies so far investigating the potential role of brain MRI findings in the management of AF. In this review, we summarise the main findings on MR imaging in AF cohorts and explore the available evidence (according to a literature search undertaken in February 2014; see online supplementary material) to support its use to better tailor the management of patients with AF (particularly by predicting the future risk of stroke including ICH).

BRAIN IMAGING FINDINGS IN HEALTHY INDIVIDUALS

Asymptomatic incidental abnormalities of the brain on MRI are common in the general population and include areas of 'silent' infarction, white matter hyperintensities (WMH), cerebral microbleeds (CMB), intracranial aneurysms, asymptomatic vessel stenosis and (mostly benign) tumours[7 9–24] (table 1, figure 1). These findings, particularly when detected incidentally, may present management challenges.[25]

Silent brain infarction (SBI) is a term for radiological evidence of focal arterial ischaemia without any obvious clinical correlation. The commonly used term 'silent stroke' is also potentially misleading as patients with SBI may suffer from subtle cognitive or physical deficits on careful evaluation.[26] According to epidemiological studies using brain MRI, 8–28% of the general population, 2.5–4% of persons aged 40–60 years and 18–40% of octogenarians were found to have abnormalities consistent with brain infarction without evident clinical

Table 1 Prevalence of incidental brain abnormalities in populations undergoing brain MR imaging

	General population (%)	AF patients without prior stroke (%)	AF patients with prior stroke (%)	References
'Silent' brain lesion(s)	7–28	28–90	N/A	9–13, 22, 23
White matter hyperintensities	5–96	N/A	23*	14–16, 24
Cerebral mircobleed(s)	5–15	10–20	7–32	7, 17–20
Cerebral aneurysm(s)	0.4–1.8			10, 21
Major vessel stenosis	0.5			10
(Mostly benign) brain tumour(s)	0.7–1.6			10, 21

*Patients with 'cardioembolic' stroke; this study also included many patients with brain CT only.
AF, atrial fibrillation.

symptoms[9 10] (figure 1A). A recent review demonstrated marked variation in MRI characteristics and diagnostic criteria used for SBI,[27] so the true prevalence in the population is hard to determine.

WMH-also termed leukoaraiosis-are common in the elderly (table 1, figure 1B). The underlying pathophysiology of WMH is poorly understood, but they are generally considered, at least in older populations, to be an imaging manifestation of sporadic small vessel disease (SVD), a disease process affecting the small (40–200 μm diameter) arterial vessels, commonly referred as arteriolosclerosis, lypohyalinosis or fibrinoid necrosis depending on the severity. Although often attributed to arterial injury due to hypertension, alternative mechanisms for sporadic SVD and the imaging correlate WMH include hypoxia or ischaemia, endothelial dysfunction or embolism.[28] It must also be appreciated that other disease process can cause MRI changes indistinguishable from SVD, for example, inflammatory disorders or leukodystrophies, but these can usually be diagnosed according to the clinical picture.

CMB are small homogenous round hypointense areas on blood-sensitive T2*-weighted gradient-recalled echo or susceptibility weighted MRI sequences[29] (figure 1C/2C/2D), corresponding to areas of hemosiderin deposition, suggesting limited focal prior bleeding.[30] Asymptomatic CMBs can be detected by MRI in about 5–15% of the general population with an age-dependent increasing prevalence (table 1). In some populations, a strong correlation between degree of WMH and presence of CMBs, age and prior use of antithrombotic medications has been reported.[20 31]

Importantly, the appearance and extent of pathological MRI findings depends on field strength, coil technology, the spatial resolution and technical details of the sequence like voxel size.[32 33]

BRAIN IMAGING FINDINGS IN PATIENTS WITH AF

MRI data on SBI in specific AF cohorts are limited. Nevertheless, SBI were observed in 28–90% of patients with AF undergoing brain MRI in small case series (table 1). The prevalence of SBI was increasing with patients' age but was not different in paroxysmal or persistent AF if reported. AF may cause SBI by causing emboli to the brain or by AF-related hypoperfusion, but the underlying pathogenesis remains poorly understood. AF was an independent risk factor for SBI in the Framingham Offspring study[34] and in several other studies (heterogeneous in population and design[13 22 23 34–36]; table 2), but the available data are not fully consistent. Furthermore, the patients with AF enrolled in these cohort studies had important competing risk factors for cerebral emboli, and the majority of these SBI were likely due to SVD and not AF-related.

The prevalence of WMH has not been specifically reported in AF cohorts (table 1). The evidence of a specific association between AF and WMH is inconsistent and is also derived from heterogeneous populations using differing study designs[16 23 37–39] (table 3). Proposed mechanisms associating AF with WMH are hypoperfusion and microinfarction. However, given the inconsistencies, it is not clear as to whether a true association exists.

CMBs have been frequently found in patients with AF with or without prior stroke (table 1). One study in patients with AF with ischaemic stroke showed a significant correlation between number and location of CMBs and the $CHADS_2$/CHA_2DS_2-VASc score, while age was the only independent predictor for the presence of CMBs.[17] Any association between AF

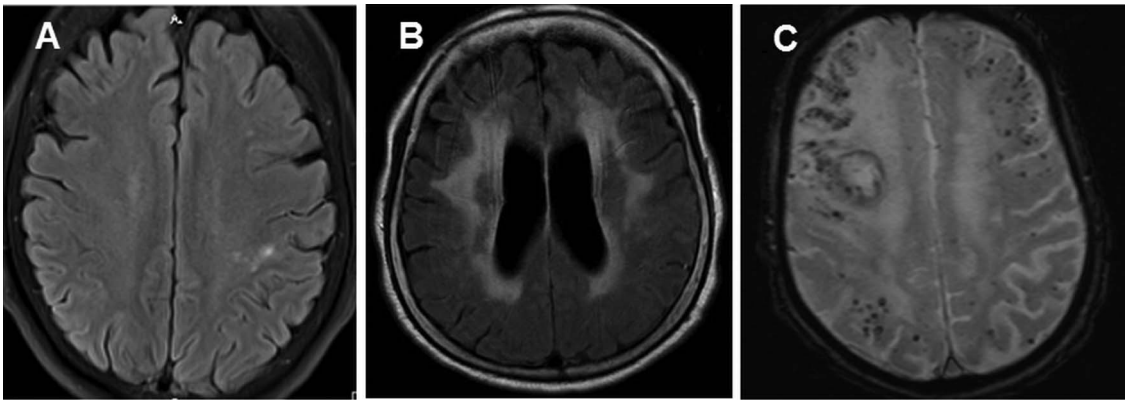

Figure 1 Pathological brain MRI findings: FLAIR image at 3.0 T demonstrating silent brain lesions in an asymptomatic patient with atrial fibrillation (A). FLAIR image at 3.0 T illustrating confluent white matter hyperintensities indicating severe leukoaraiosis (B). T2* image at 1.5 T demonstrating multiple cerebral microbleeds and a prior chronic intracerebral haemorrhage in a patient with cerebral amyloid angiopathy (C).

Table 2 Studies assessing association between atrial fibrillation (AF) and MRI-detected silent brain infarction (SBI)

Population (number of participants (participants with AF))	Study design	Findings	References
Population-based autopsy series (n=966 (NA))	Retrospective case series	AF significantly associated with SBI (OR 2.46 (95% CI 1.07 to 5.68))	35
Population based (n=2040 (45))	Prospective	AF significantly associated with SBI (OR 2.16 (95% CI 1.07 to 4.40))	34
Diabetic patients (n=464 (NA)) and non-diabetic patients (n=240 (NA))	Longitudinal matched pair	AF significantly associated with SBI (OR 4.44 (95% CI 2.42 to 8.16))	36
Healthy subjects (n=1200 (400))	Longitudinal matched pair	AF significantly associated with SBI (OR 3.16 (95% CI 1.29 to 7.74))	22
Hospitalised non-stroke patients (n=142 (71))	Case control	AF significantly associated with SBI >5 mm diameter (OR 2.53 (95% CI 1.21 to 5.3))	23
Patients referred to a cardiologist (n=270 (180))	Case control	AF significantly associated with SBI (OR 7.2 (95% CI 2.3 to 22.3))	13

and CMB[40] seems likely to reflect vascular risk factors associated with AF and CMB, for example, age and hypertension.

IMPACT OF BRAIN IMAGING FINDINGS TO PERSONALISE AF THERAPY

A framework for how brain MRI may influence treatment decisions is shown in table 4[17 41–44 57] and figure 2. However, it is clear that at present the evidence for the predictive value of MRI findings in managing AF in clinical practice remains limited.

In general, SBI are associated with an increased risk of overt ischaemic stroke and an increased risk of worsening of cognitive function, which more than doubles the risk of dementia in population cohorts.[26 45] Comparable data specifically in patients with AF are not yet available[22] despite the fact that cognitive decline in AF cohorts is reported,[46] particularly after ischaemic stroke.[47] Available evidence from clinical studies[13 48] does not yet prove that optimising treatment of AF reduces the burden of SBI or cognitive decline.[7] CT-detected SBI in patients with AF with clinically evident ischaemic stroke indicated a slightly higher risk for recurrent ischaemic stroke in the European Atrial Fibrillation Trial (EAFT), but this was not statistically significant (HR 1.18 (95% CI 0.79 to 1.77)).[41] However, a recent retrospective MRI study demonstrated a HR of 1.79 (95% CI 1.09 to 2.93) for first time clinically evident stroke during a mean follow-up of 67 months in patients with AF with SBI compared with patients with AF without SBI.[22] Further data in patients with AF with or without prior stroke but with SBI are not yet available.

Therefore, imaging-detected SBI in patients with AF cannot yet be regarded as a proven risk factor for AF-related future stroke or cognitive impairment (table 4). Furthermore, there is currently no evidence to support the inclusion of SBI as evidence of 'stroke' in clinical risk prediction scores. It is clear that further prospective studies of SBI in AF are required to determine the clinical relevance of these common lesions for prognosis in AF cohorts.

WMH are associated with a higher mortality rate, cognitive dysfunction as well as an increased risk of ischaemic stroke and ICH in population-based studies.[28 49 50] Furthermore, a subgroup analysis of the Stroke Prevention In Reversible Ischemia Trial (SPIRIT)[42] and a small case–control study[51] established an association between CT-detected leukoaraiosis and ICH in patients with ischaemic stroke without AF receiving warfarin, but the high target INR (3–4.5) and the specific population included in this study do not allow generalisability to current practice in AF cohorts (table 4).

The small amount of available evidence does not support stopping or not starting OAC in patients with AF with additional stroke risk factors and WMH. In patients with AF with WMH, treatment of modifiable risk factors for stroke, SVD and ICH (eg, arterial hypertension, alcohol consumption, etc) is strongly encouraged. Whether direct OACs (DOACs) have a lower bleeding risk in patients with AF with WMH remains to be established.

CMBs are associated with an increased risk of ischaemic stroke and spontaneous ICH in both the general population[18] and in ischaemic stroke or transient ischemic attack (TIA) cohorts.[52] In a pooled meta-analysis, the OR for ICH in stroke or TIA cohorts overall was 8.52 while the OR for ischaemic stroke was 1.55. Data in cohorts exposed to OAC are limited but suggest a relationship between CMBs and warfarin-associated ICH in cross-sectional case–case comparisons.[53] A prospective cohort study of 550 patients with

Table 3 Studies assessing associations between atrial fibrillation (AF) and MRI-detected white matter hyperintensities (WMH)

Population (number of participants (participants with AF))	Study design	Findings	References
Hospitalised non-stroke patients (n=142 (71))	Case control	AF significantly associated with deep and subcortical but not with periventricular WMH	23
Population based (n=1077 (28))	Random selection from two observational studies	AF significantly associated with periventricular WMH (RR 2.2 (95% CI 1.0 to 5.2)) but not subcortical WMH	37
Acute ischaemic stroke (n=523 (77))	Retrospective analysis of prospective study	AF not associated with WMH	38
Elderly subjects in memory clinic (n=177 (NA))	Prospective	AF not associated with severe deep or periventricular WMH	39
Ischaemic stroke (n=1601) and memory clinic attendees (n=313)	Case–control, also including 1049 patients with brain CT	AF not associated with WMH (OR 1.09 (95% CI 0.55 to 2.16))	16

Table 4 Potential relevance of brain MRI for treatment with OAC in selected atrial fibrillation cohorts

	'Silent' brain infarcts	White matter hyperintensities	Cerebral microbleeds (CMBs)	Comments	References
HAS-BLED ≥3 in patients after ischaemic stroke or TIA	(+)*	+**	+***	* Non-significant trend for recurrent stroke in EAFT. ** If severe: Increased bleeding risk in SPIRIT (target-INR 3–4.5). *** Multiple CMBs may be a risk factor for future intracerebral haemorrhage but risk may differ according to population.	17 41 42
Gait disturbance or falls	?	+*	+	* Helps to differentiate between vascular gait disorders and other types of gait disturbance. Severe white matter disease and frequent falls may increase ICH risk.	
Cognitive impairment or dementia	+*	+*	+**	* Helps to evaluate the contribution of SVD to cognitive impairment. ** Multiple CMBs suggesting CAA—may increase the risk of intracerebral haemorrhage, though limited specific data in this population.	44
Recent intracerebral haemorrhage	?	+	++	Localisation of CMBs (lobar vs basal ganglia) will help to assess risk of recurrence: higher for presumed CAA-related lobar ICH. Graded relationship between number of CMBs and ICH risk has been reported in CAA. Consensus recommendation is to avoid OAC in probable CAA-related ICH wherever possible.	43 57

Note that there is no evidence from prospective randomised trials to support the following perspectives.
EAFT, European Atrial Fibrillation Trial; SVD, small vessel disease.
*, ** and *** represent sentinels.

ischaemic stroke or TIA in Asia showed that baseline CMBs were related to future ICH risk over 3.1 years,[17] while the $CHADS_2$ and CHA_2DS_2-VASC scores were not, suggesting that the MRI provided additional prognostic information. A recent study, also in ischaemic stroke and TIA and non-valvular AF, found that during a mean follow-up period of 24.7 months, 29 (10.4%) of 204 patients developed new CMBs, and that increasing age, increased WMH and prior CMBs were significantly associated with development of new CMBs. Thus, anticoagulation may increase the probability that an incident CMB evolves into a 'macrobleed' (symptomatic larger ICH).[54]

Given the known association of CMBs with bleeding-prone arteriopathies (eg, hypertensive arteriopathy, cerebral amyloid angiopathy)[55] (table 4, figure 2), the presence and number of CMBs may have important implications for increased ICH risk in patients with AF with ischaemic stroke or TIA.

CMBs may also have particular relevance in survivors of ICH with an indication for long-term anticoagulation due to AF; recent reports suggest that this dilemma faces 30% of ICH survivors[56] and that there is a low use of anticoagulants in this cohort due to clinical uncertainty, with a lack of validated risk predictors. Previous studies suggest that the burden of CMBs is a predictor of ICH recurrence in individuals with probable cerebral amyloid angiopathy[57] and that CMBs may interact with antithrombotic treatments (at least for antiplatelet drugs) to increase the risk of further ICH.[58] Thus, a pattern of CMBs suggesting cerebral amyloid angiopathy (CAA) (particularly if the CMB number is large) may present a strong caution against anticoagulation (figure 2C,D), but further prospective data in larger representative ICH cohorts are needed.

Another recent study investigated the risk of future symptomatic ICH in patients with probable CAA with only CMBs (including those patients presenting with cognitive impairment) found a considerable risk of incident ICH, which was increased by use of warfarin after adjusting for other confounders.[44] Nevertheless, data are currently limited and it remains uncertain as to whether CMBs add to existing clinical risk prediction scores. Further prospective studies are needed to assess how CMBs influence OAC-related ICH risk in the different clinical populations including ischaemic stroke/TIA, ICH and those with cognitive impairment.

One recently identified new imaging marker associated with sporadic SVD (in particular CAA) is cortical superficial siderosis (cSS). cSS has been linked to an increased risk of future ICH

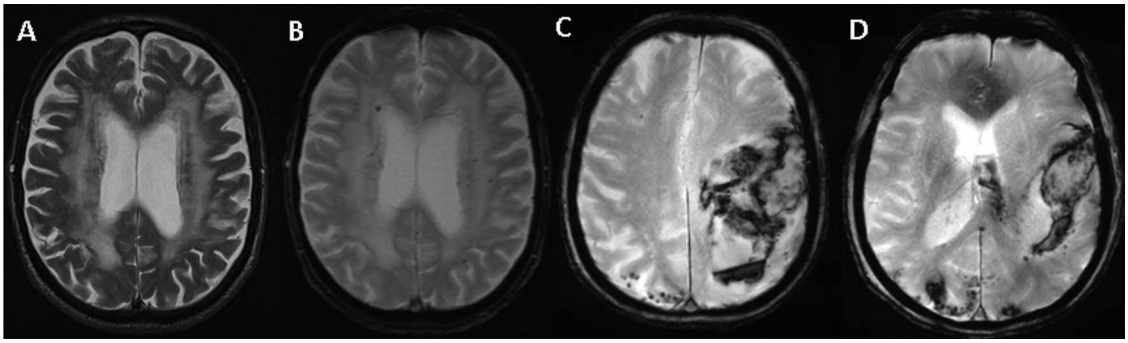

Figure 2 Atrial fibrillation patients deemed unsuitable for oral anticoagulation (corresponding to table 4). T2 (A) and T2* image (B) at 1.5 T demonstrating confluent white matter hyperintensities and cerebral microbleeds in an atrial fibrillation patient with recent TIA, cognitive impairment, unsteady gait, frequent falls and a HAS-BLED score of 4. T2* images (C/D) at 3.0 T demonstrating an acute lobar haemorrhage and multiple cerebral microbleeds in an atrial fibrillation patient with suspected cerebral amyloid angiopathy.

risk in CAA cohorts,[59] but we are not aware of any specific data on any interaction between cSS and the use of antithrombotic agents, and there are no studies available in AF cohorts.

LIMITATIONS IN TERMINOLOGY AND STUDY DESIGN

A recent review on MRI studies revealed the varying definitions for cerebrovascular lesions,[27] representing a major limitation when comparing different MRI studies. It is recommended that standardised definitions be used, for example, those in recently published guidelines.[28] In addition, central MRI reading or double reads are required to validate the impact of new imaging criteria. Moreover, available evidence largely comes from patients with different ethnic backgrounds or coexisting cardiovascular risk profiles as well as case–control studies that cannot prove causality. Thus, well-designed prospective cohort studies in relevant AF populations (eg, following ICH or ischaemic stroke) are required to determine the role of MRI in risk stratification of OACs. One such ongoing study is CROMIS-2 (see http://www.ucl.ac.uk/cromis-2), a multicentre UK-based inception cohort study in patients with ischaemic stroke or TIA associated with AF.[54]

CONCLUSION AND RECOMMENDATIONS

The increased use of brain MRI and the advancements in MRI technology has led to an increased knowledge of (often asymptomatic) findings related to cerebrovascular disease that has a prognostic impact, as demonstrated at least in patient cohorts without AF. Whether brain MRI has the potential to improve the personalised management of patients with AF by predicting the individual risk for ICH and (recurrent) ischaemic stroke remains to be established in large prospective follow-up studies using standardised brain MRI.

However, even today, brain MRI may be useful to identify subsets of patients with AF at increased risk for intracerebral bleeding, particularly in survivors of ICH (table 4, figure 2). In survivors of lobar ICH, long-term oral anticoagulation should probably be avoided, especially if there is MRI evidence of cerebral amyloid angiopathy in the form of multiple lobar CMBs. However, the predictive value of brain MRI findings in patients with AF needs to be established in large randomised trials of appropriate sample size. Therefore, treatment decisions in clinical practice should still be based on data from established validated risk scores and large randomised trials in the majority of patients with AF. Although present knowledge and MRI-associated costs do not support the routine use of brain MRI in asymptomatic patients with AF, as more data emerge MRI may become a useful way to stratify some groups of patients with AF (eg, those with previous stroke or cognitive impairment) and individualise their treatment.

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