Clinical relevance of neuroimaging biomarkers of small vessel disease in relation to intracranial haemorrhage

THESIS DISSERTATION

by

Duncan R. WILSON

A thesis submitted
in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Clinical Neurology

University College London

Stroke Research Centre

Department of Brain Repair and Rehabilitation

May 2018

I, Duncan R Wilson confirm that the work presented in this thesis is my own; where data is derived from other sources, I confirm this has been indicated in the thesis.

ACKNOWLEDGEMENTS

Firstly, I would like to thank UCL for providing me an opportunity to study and learn in such an illustrious institution. I attended multiple teaching courses on a variety of topics in addition to maintaining my clinical skills, all of which has improved my ability as a medical doctor.

I am in great debt to many people. Foremost my principal supervisor Professor David Werring. Having the opportunity to work with him on CROMIS-2 not only provided me with a goldmine of research data, but also allowed me to understand the inner running of a large medical study. His guidance during my PhD has been exceptional, allowing me sufficient autonomy yet keeping me focused and in the right direction. He has been invaluable in honing my medical writing and attention to small details. My secondary supervisor Professor Rolf Jäger has also been a fantastic help; providing neuroimaging training in addition to numerous sub study ideas and access to radiological expertise.

Dr Gareth Ambler has been invaluable for his statistical expertise. Not only in double-checking my statistical analysis but also in providing one on one teaching in addition to UCL's statistical courses.

There are a whole host of people to whom I am further indebted; the majority of the data in my thesis has come from CROMIS-2. I am therefore truly grateful to every research practitioner and principal investigator who worked so hard to enroll so many patients. In addition, there is the CROMIS-2 team, in particular, Clare Shakeshaft who helped manage and curate the data and ensured the study ran smoothly.

Lastly to my lovely wife Ainsley for providing the time and support which allowed me to write my thesis.

PRINCIPAL SUPERVISOR: PROFESSOR DAVID J WERRING

SECONDARY SUPERVISOR PROFESSOR HANS R JÄGER

ABSTRACT

Introduction: Small vessel disease is the underlying cause of most spontaneous (non-traumatic) ICH. Cerebral imaging markers of small vessel disease, particularly cerebral microbleeds (CMBs) and white matter hyperintensities of presumed vascular origin (WMH) offer clinicians and researchers an opportunity to further understand the pathogenesis and risk of ICH in patients with stroke. In this thesis I present a portfolio of studies aimed to show the clinical relevance of neuroimaging biomarkers of small vessel disease in relation to intracerebral haemorrhage (ICH).

Methods: I ascertained patients primarily through the Clinical Relevance Of Cerebral Microbleeds In Stroke (CROMIS-2) study, a multicentre prospective observational study recruiting patients with both ICH and patients with ischaemic stroke associated with atrial fibrillation (AF) from 79 centres throughout the UK and one in the Netherlands. Data was also collected locally from ICH patients seen in the UCL Hospital's comprehensive stroke service, international collaborations and through the meta-analysis of published studies.

Main findings: 1) CMBs are associated with an increased relative risk of subsequent ICH in patients with ischaemic stroke (primarily treated with antiplatelet drugs) and the ICH risk increases more steeply with CMB burden than does the risk of ischaemic stroke; 2) In patients with AF anticoagulated after recent ischaemic stroke or TIA, CMB presence is independently associated with symptomatic intracranial haemorrhage risk, improves the predictive ability of clinical risk scores, and can inform anticoagulation decisions; 3) The presence of cerebral small vessel disease is associated with a lower risk of a macrovascular cause of ICH; 4) Lobar ICH location (compared to non-lobar location) is associated with higher recurrent ICH risk and lower new ischaemic stroke risk; 5) The CHA_2DS_2VASC score has similar modest predictive value in estimating the risk of ischaemic stroke in patients with ICH and concurrent AF, but risk prediction was not improved by adding SVD presence.

Conclusion: These studies confirm the clinical relevance of neuroimaging markers of small vessel disease in the diagnosis and prediction of intracranial haemorrhage and provide a framework for future research

LIST OF PUBLICATIONS RELATED TO WORK

DESCRIBED IN THIS THESIS

Wilson D, Ambler G, Shakeshaft C, Brown MM, Charidimou A, Al-Shahi Salman R, Lip GYH, Cohen H, Banerjee G, Houlden H, White MJ, Yousry TA, Harkness K, Flossmann E, Smyth N, Shaw LJ, Warburton E, Muir KW, Jäger HR, Werring DJ Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack: multicentre observational cohort study. Lancet Neurology. 2018 Jun;17(6):539-547.

Wilson D, Ogungbemi A, Ambler G, Jones I, Werring DJ, Jäger HR. Developing an algorithm to identify patients with intracerebral haemorrhage secondary to a macrovascular cause. European Stroke Journal. 2017 Sep;(4):369-376

Wilson D, Hostettler IC, Ambler G, Banerjee G, Jäger HR, Werring DJ. Convexity subarachnoid haemorrhage has a high risk of intracerebral haemorrhage in suspected cerebral amyloid angiopathy. J Neurol. 2017 Apr;264(4):664-673

Wilson D, Chatterjee F, Farmer SF, Rudge P, McCarron MO, Cowley P, Werring DJ. Infratentorial superficial siderosis: Classification, diagnostic criteria, and rational investigation pathway. Ann Neurol. 2017 Mar;81(3):333-343

Wilson D, Werring DJ. Antithrombotic therapy in patients with cerebral microbleeds. Curr Opin Neurol. 2017 Feb;30(1):38-47

Wilson D, Charidimou A, Ambler G, Fox ZV, Gregoire S, Rayson P, Imaizumi T, Fluri F, Naka H, Horstmann S, Veltkamp R, Rothwell PM, Kwa VI, Thijs V, Lee YS, Kim YD, Huang Y, Wong KS, Jäger HR, Werring DJ. Recurrent stroke risk and cerebral microbleed burden in ischaemic stroke and TIA: A meta-analysis. Neurology. 2016 Oct 4;87(14):1501-1510

Wilson D, Werring DJ. Establishing the "meaning" of microbleeds: Clinical context or lobar microbleed burden? Alzheimers Dement. 2016 Jan;12(1):85-6. doi: 10.1016/j.jalz.2015.09.004

Wilson D, Jäger HR, Werring DJ Anticoagulation for Atrial Fibrillation in Patients with Cerebral Microbleeds. Curr Atheroscler Rep. 2015 Aug;17(8):47

Wilson D, Adams ME, Robertson F, Murphy M, Werring DJ. Investigating intracerebral haemorrhage. BMJ. 2015 May 20;350:h2484

Wilson D, Charidimou A, Werring DJ Advances in understanding spontaneous intracerebral haemorrhage: insights from neuroimaging. Expert Rev Neurother. 2014 Jun;14(6):661-78

Wilson D, Charidimou A, Werring DJ. Use of MRI for Risk Stratification in Anticoagulation Decision Making in Atrial Fibrillation: Promising, but More Data are Needed for a Robust Algorithm. Front Neurol. 2014 Jan 20;5:3

Kongbunkiat K, **Wilson D**, Kasemsap N, Tiamkao S, Jichi F, Palumbo V, Hill MD, Buchan AM, Jung S, Mattle HP, Henninger N, Werring DJ. Leukoaraiosis, intracerebral haemorrhage, and functional outcome after acute stroke thrombolysis. Neurology. 2017 Feb 14;88(7):638-645

Charidimou A, **Wilson D**, Shakeshaft C, Ambler G, White M, Cohen H, Yousry T, Al-Shahi Salman R, Lip G, Houlden H, Jäger HR, Brown MM, Werring DJ The Clinical Relevance of Microbleeds in Stroke study (CROMIS-2): rationale, design, and methods. Int J Stroke. 2015 Oct;10

Haeusler KG, **Wilson D**, Fiebach JB, Kirchhof P, Werring DJ. Brain MRI to personalise atrial fibrillation therapy: current evidence and perspectives. Heart. 2014 Sep 15;100(18):1408-13

Hilkens NA, van Asch CJJ, Werring DJ, **Wilson D**, Rinkel GJE, Algra A, Velthuis BK, de Kort GAP, Witkamp TD, van Nieuwenhuizen KM, de Leeuw FE, Schonewille WJ, de Kort PLM, Dippel DWJ, Raaymakers TWM, Hofmeijer J, Wermer MJH, Kerkhoff H, Jellema K, Bronner IM, Remmers MJM, Bienfait HP, Witjes RJGM, Jäger HR, Greving JP, Klijn CJM; DIAGRAM study group. Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score. J Neurol Neurosurg Psychiatry. 2018 Jan 18. pii: jnnp-2017-317262

Charidimou A, Schmitt A, **Wilson D**, Yakushiji Y, Gregoire SM, Fox Z, Jäger HR, Werring DJ. The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS): Development and assessment of reliability. J Neurol Sci. 2017 Jan 15;372:178-18

CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS USED IN THIS THESIS

ICH	Intracerebral Haemorrhage
SVD	Small Vessel Disease
APOE	Apolipoprotein E
CAA	Cerebral Amyloid Angiopathy
CADASIL	Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
CARASIL	Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
CR1	Complement Component Receptor
MRI	Magnetic Resonance Imaging
PET	Positron emission tomography
TIA	Transient Ischaemic Attack
HR	Hazard Ratio
AF	Atrial Fibrillation
CROMIS	Clinical Relevance Of Microbleeds In Stroke
cSS	cortical Superficial Siderosis
TFNE	Transient focal neurological episodes
WMH	White Matter Hyperintensities
DWIHL	Diffusion Weighted Imaging Hyperintense Lesions
PVS	MRI visible Perivascular Spaces
RCT	Randomised control trial
NOAC	Non-Vitamin K Oral Anticoagulant (Interchangeable with DOAC)
RR	Risk Ratio
IS	Ischaemic stroke
SWI	Susceptibility Weighted Imaging
HTN	Hypertension
GRE	Gradient Recalled Echo
IQR	Interquartile Range
SD	Standard Deviation

ARWMC	Age Related White Matter Changes
DOAC	Direct Oral Anticoagulants (synonymous with NOAC)
CT	Computed tomography
CTA	Computed Tomography Angiography
IADSA	Intra Arterial Digital Subtraction Angiography
OR	Odds Ratio
SAH	Subarachnoid Haemorrhage
ROC	Receiver Operated Curve
INR	International Normalised Ratio
ETOH	Ethanol
mRS	modified Rankin Scale
NIHSS	National Institute for Health Stroke Scale
NOAC	Non-vitamin K (or Novel) Oral Anticoagulant
TF	Tissue Factor
HE	Haematoma Expansion
IVH	Intraventricular Haemorrhage
GCS	Glasgow Coma Scale
PCC	Prothrombin complex concentration
AIS	Acute Ischaemic Stroke
ASL	Arterial Spin Labelling
TTR	Time in therapeutic range
RESTART	Restart or STop Antithrombotics. Randomised Trial
SoSTART	Start or STop Anticoagulants Randomised Trial
RESTART-FR	Restart or STop Antithrombotics. Randomised Trial
STATICH	Study of Antithrombotic Treatment After Intracerebral Haemorrhage
	NASPAF-ICH NOACs for Stroke Protection in Patients with Atrial Fibrillation and Intracerebral Haemorrhage
A3-ICH	Avoiding Anticoagulation After Intracerebral Haemorrhage
APACHE-AF	Apixaban Versus Antiplatelet Drugs or no Antithrombotic Drugs After Anticoagulation-associated Intracerebral Haemorrhage in Patients With Atrial Fibrillation: A Randomised Phase II Clinical Trial

HASBLED Hypertension, Abnormal renal function, Abnormal liver function, Alcohol, Stroke, Bleeding history, Labile blood pressure, Elderly, Drugs

CHA_2DS_2Vasc Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, Sex

BOLD Blood oxygenation level dependency

PART 1

INTRODUCTION

1.0 Introduction to Intracerebral haemorrhage

Intracerebral haemorrhage (ICH) - bleeding into the brain parenchyma is the most devastating form of stroke, with a case fatality approaching 50% at one month (1) and high morbidity in survivors: 32 % being functionally dependent at one year. (2) A meta-analysis involving 122 studies of longer-term prognosis found a pooled one-year survival of 46%, and five-year survival of only 29% (3).

ICH accounts for 10-15% of strokes in Western populations, and up 40% in some Asian populations. (4, 5) Whilst the incidence of ischaemic stroke has fallen (6), the incidence of ICH has remained static in recent decades (4). Indeed, there is evidence that the incidence of ICH in the elderly and in association with oral anticoagulant use is increasing, (7-9) making it a key research challenge in cerebrovascular disease.

ICH may result from a wide range of potential causes (10). Conventionally ICH is classified as ‘traumatic’ or ‘spontaneous’ (i.e. ‘non-traumatic’). The spontaneous group is further subdivided into ‘secondary’ (due to identified causes including bleeds into tumors, cavernomas, arterio-venous malformations, central nervous system infection, cerebral venous sinus thrombosis, bleeding disorders, etc.) or ‘primary’ if there is no obvious underlying cause. With cumulative advances in neuroimaging and histopathological correlates it is now generally accepted that the main processes underlying so-called ‘primary ICH’ are intrinsic diseases affecting cerebral small vessels (generally a few hundred microns and up to about 1-2mm) – usually collectively termed small vessel disease (SVD). This understanding has led a recent large international consensus group for standardized definitions in neuroimaging markers of small vessel disease to suggest the term ‘spontaneous intracerebral haemorrhage presumed to be due to SVD’ be preferable to primary ICH (11). However, it is critical to exclude “secondary” structural causes of ICH, including macrovascular causes (e.g. arterio-venous malformations, aneurysms, and dural arteriovenous fistulae), which can be treated.

The “reference standard” for detection of a macrovascular cause is intra-arterial digital subtraction angiography (IADSA) or neurosurgery. IADSA is invasive, requires skilled

operators and is associated with a small but appreciable mortality and morbidity, especially in acute ICH (12). Selecting which ICH patients have a sufficiently high likelihood of a macrovascular cause to recommend IADSA is a common and important clinical question. Current practice varies widely (13): typically, the presence of pre-ICH hypertension, deep location of ICH and age are used as indicators of SVD to select patients unlikely to require IADSA(13), but the evidence supporting this is scant and often conflicting (14-16).

1.1 Causes of Intracerebral haemorrhage

A discussion of the nature of causation is beyond the scope of this thesis, but a 'cause' can most simply be defined as something, which affects the prevalence, likelihood or clinical effect of a disease. For ICH, contributory causes include the underlying SVD processes, but also 'risk factors' (e.g. hypertension, diabetes, lipid profile, smoking, alcohol use, etc.) which may influence the clinical expression of these SVD processes. The challenge with many studies of ICH (particularly cross-sectional data) is that they can show associations but cannot provide proof (or direction) of causality. Whether an association reflects causation can be considered according to the strength of association; consistency; specificity; dose-response relationship; biological plausibility and consistency with disease natural history (17).

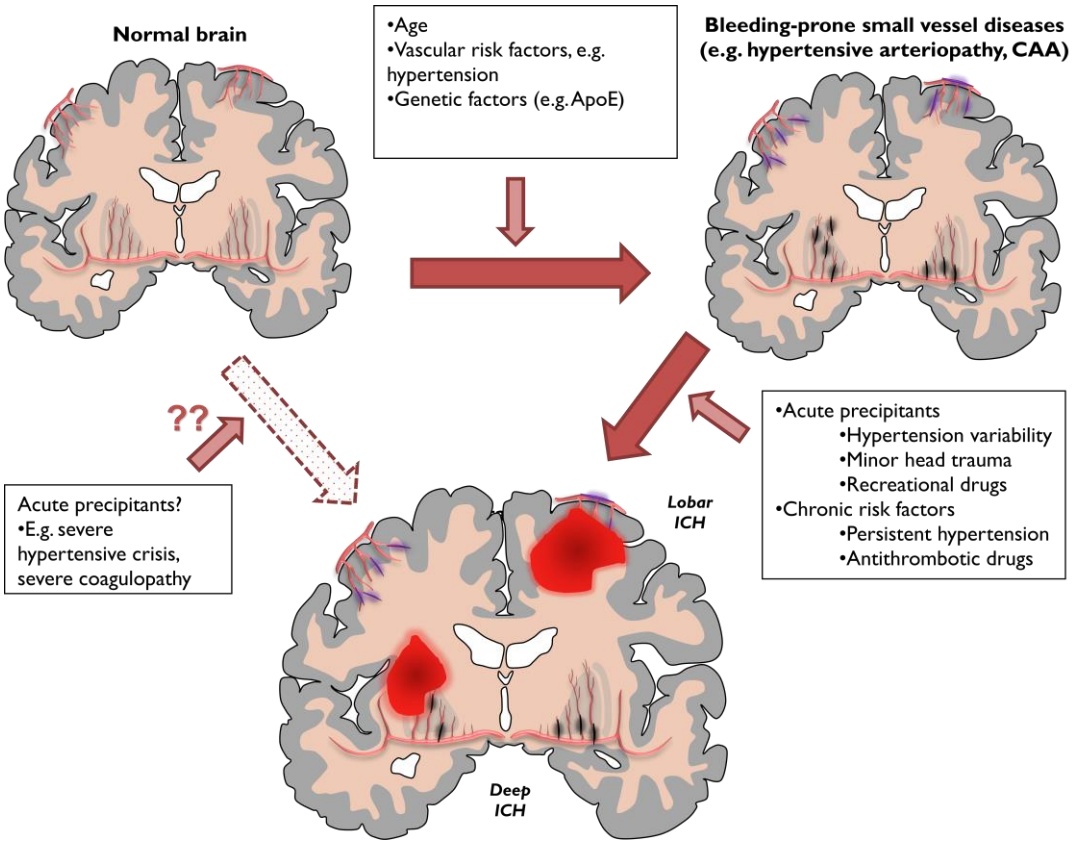
SVD is highly prevalent in older populations(18) yet ICH is much less common. Thus, as in other types of stroke, spontaneous ICH is likely to result from an interplay between environmental and individual patient (e.g. genetic) factors relating to the expression of SVD. Indeed, recent data suggest that genetic variation plays a significant role in ICH risk and outcome. (19) It was estimated that 44% of ICH risk variance was accounted for by genetic risk factors, with a greater contribution of genetic factors (especially apolipoprotein E [APOE] alleles) to lobar ICH than deep ICH. (19)

One model of ICH causation is that multiple acute or chronic risk factors (e.g. age, sustained hypertension or short-term blood pressure fluctuations, antithrombotic drugs (antiplatelet agents or anticoagulants), serum cholesterol levels or statin use, minor head trauma, etc.) interact with vulnerable damaged small vessels (subject to the influence of genetic or other individual patient factors), which, when a certain threshold is exceeded, ultimately rupture to culminate in ICH as represented in figure 1.

Indeed, a population-based study suggested that ICH may result from short-term increases in blood pressure prior to the event (over weeks to months), by contrast with ischaemic

stroke where blood pressure is more stable (20). This finding suggests that consistent long-term blood pressure control may be especially important in reducing the risk of ICH.

Figure 1 Aetiology of ICH



From Wilson et al: Expert Rev Neurother. 2014 Jun;14(6):661-78

1.2 Epidemiology of ICH

The epidemiology of ICH has changed over the years with an aging population, more aggressive treatment for hypertension and increasing use of anticoagulation. It may well still be changing: with the advent of the direct anticoagulants, we may expect to see an even higher use of anticoagulants in elderly patients. Although these drugs have about half the ICH risk compared to warfarin(21), their increased use may still overall lead to a higher prevalence of ICH in the elderly population. This is of importance as higher age is associated with worse outcomes (22, 23). One paper comparing ICH in the very elderly found those aged greater than 85 years had increased incidence of neurological deficit at

hospital discharge (89% vs. 58%, P < .005), and in-hospital mortality (50% vs. 27%, P < .01) than those younger than 85 (22). However, the cut off age could be considered arbitrary, and there was no significant difference in either neurological deficit or mortality when comparing those aged greater than 85 to those aged between 65 and 85.

Whilst global ICH rates have remained stable (4) improved hypertension control seem to be offset by the increasing number of anticoagulation and cerebral amyloid angiopathy (CAA) related haemorrhages (7-9). Large cohorts, each over a 20-year period from Oxfordshire and Dijon have shown a decrease in the incidence of ICH in the younger age group (<75 years, <65 years respectively) by roughly 50% (7, 8); however the Dijon cohort reported an 80% increase in ICH incidence in those aged over 80 years.(7) A large study from Cincinnati looking at anticoagulation-related ICH over a 10 year period has shown that anticoagulant-related haemorrhage has increased five-fold (9), which closely corresponds to the four-fold increase in anticoagulant (Warfarin) use (per capita) over the same period (9)

1.3 Role and clinical relevance of anticoagulation in ICH

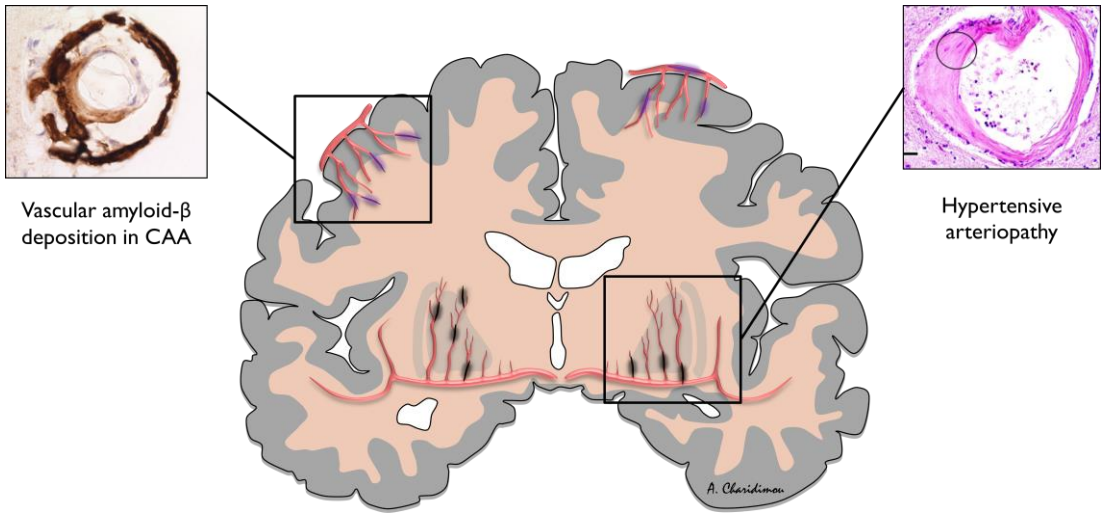
Anticoagulants should not 'cause' ICH *per se* as they only impair the body's ability to form thrombin clots (at different points in the coagulation cascade depending on the medication), and do not lyse formed clots. It is hypothesized, however, that in vulnerable individuals (e.g. those with SVD) where a bleed has occurred, anticoagulants lead to larger ICH volumes due to impaired haemostasis. If this is the case then patients with ICH on anticoagulants should have larger hematoma volumes, and more hematoma expansion, than those not taking oral anticoagulants. Indeed, anticoagulation is generally associated with larger baseline haematoma volumes (24-30) and hematoma growth (29-31): in studies with over 100 patients which investigate this relationship (18-26), all but one (32) show a significant relationship between anticoagulation and hematoma size. One study revealed an association between anticoagulation intensity (INR) and the volume of deep ICH but not for lobar ICH (25) suggesting differing underlying pathology (e.g. amyloid angiopathy and hypertensive arteriopathy) in different brain regions may respond differently to anticoagulation. This finding has not been replicated, however, and further studies are warranted. Three studies to date show that hematoma expansion is increased by

anticoagulation; two of these studies were observational hospital-based studies (30, 31) without standardized CT timing scanning. Furthermore, neuroimaging characteristics and outcomes need to be explored between non-vitamin K oral anticoagulant-related ICH (which do not affect the extrinsic coagulation pathway) and vitamin K oral anticoagulant-related ICH.

2.0 Introduction to small vessel disease

Cerebral small vessel disease describes a group of pathological processes with various causes which affect the small vessels of the brain, namely: the small arteries, arterioles, venules, and capillaries (33). Most age-related small vessel damage is secondary to one of two main SVD processes (figure 2): (1) *an arteriolar process often related to aging and other common vascular risk factors (e.g. hypertension and diabetes), characterised pathologically by lipohyalinosis, arteriolosclerosis or fibrinoid necrosis, and typically affecting the small perforating end-arteries of the deep grey nuclei and deep white matter (often termed "hypertensive arteriopathy")*; and (2) sporadic cerebral amyloid angiopathy (CAA), a disease process affecting superficial cortical and leptomeningeal vessels through the deposition of amyloid β. Less commonly, ICH occurs in the context of much rarer genetic diseases (familial cerebral amyloid angiopathies, Collagen 4A1 mutations, Fabry's disease, CADASIL, CARASIL, etc.) or cerebral and systemic vasculitides, which will not be discussed in this thesis. A classification of small vessel diseases with their relevance to ICH is shown in Table 1

Figure 2 Common subtypes of small vessel disease



From Wilson et al: Expert Rev Neurother. 2014 Jun;14(6):661-78

Table 1 Types of SVD, histopathology, the prevalence of cerebral small vessel disease and relationship to ICH

Name	Histology	Prevalence	Strength of relationship to intracerebral haemorrhage
Arteriolosclerosis **Common sporadic SVD** **Hypertensive arteriopathy**	Arteriolosclerosis Lipohyalinosis Fibrinoid necrosis Microatheroma Microaneurysms	Very common	Common cause of deep or lobar ICH
Cerebral Amyloid angiopathy (CAA)	Aβ amyloid protein Dilated and disrupted walls Double barreled arterial wall	Age related 7% Those aged 65-74 18% Those aged 75-84 (34) 70% Those aged over 85 (35)	Common cause of lobar ICH
Inherited or genetic SVD **CADASIL** **COL4A1** **Fabry disease** **CARASIL**	Depends on the underlying disease	CADASIL >2 per 100000 COL4A1 Very Rare prevalence unknown Fabry disease 1 per 120000 CARASIL Very Rare, unknown	CADASIL – ICH rare (CMBs common) COL4A1 - ICH common Fabry disease – ICH rare CARASIL – ICH rare (CMBs common)
Inflammatory and Immunologically mediated SVD. (Primary angiitis CNS and systemic vasculitis)	Typical of vasculitis	Very rare	ICH common
Other (Radiation etc.)	Depends on aetiology	Rare	Rare

2.1 Sporadic cerebral amyloid angiopathy

Sporadic CAA is characterised by the progressive accumulation of amyloid-β peptide in the walls of small-to-medium-sized arteries and arterioles - and, to a lesser extent, the capillaries and veins - in the leptomeninges and cerebral cortex.(33) In the most severe form, CAA-affected small vessels become thickened and disrupted, with focal wall fragmentation and blood extravasation, with or without microaneurysmal dilatation, and sometimes show luminal occlusion. (33) The pathophysiology of sporadic CAA is poorly understood, but transgenic mouse models suggest an increased ratio of $A\beta_{40}$:$A\beta_{42}$ in the brain results in a shift of amyloid-β from brain parenchyma to the vasculature (36) (perhaps by increasing the solubility of Aβ and thus its diffusion into the vessel wall); and that vascular Aβ deposition largely results from impaired clearance of Aβ (rather than overproduction) (37), likely due to changes in the composition of capillary vascular basement membranes(38). The prevalence of CAA increases with age, especially over 60 years. (34, 39). Autopsy studies have shown CAA in more than 70% of a healthy population above the age of 90.(35, 40). CAA may vary according to ethnicity: some studies suggest a higher predilection for amyloid deposition in the frontal lobe arteries in Eastern populations (41); it has also been suggested that Eastern populations have a lower prevalence of CAA, but this may in part reflect the higher relative prevalence of hypertension and hypertensive arteriopathy in this population (41).

By contrast with other cerebrovascular diseases, CAA does not appear to be related to conventional vascular risk factors. Although hypertension may aggravate bleeding risk in CAA (42) most patients with CAA-related ICH (up to 68% in one study) are not hypertensive. (43, 44) Anticoagulation or antiplatelet treatments may also increase the likelihood of CAA-related ICH (45-48), but, apart from genetic variants there are no other known strong risk factors that increase the presence of CAA or its bleeding risk. APOE alleles are associated with CAA: A recent meta-analysis showed a dose-dependent association between APOE ε4 alleles and the presence of sporadic CAA (49). A more recent study, taking into account CAA severity, found a possible association of severe CAA with APOE ε4 but not APOE ε2, but was limited by the number of participants with ε2 genotypes (50). In addition, there have been multiple studies linking both APOE alleles (ε2

and ε4) to the risk of recurrent haemorrhage (51-54) APOE ε2 has been shown to confer greater vessel fragility (55): a large genetic association study has shown carriers of APOE ε2 had increased ICH expansion, mortality (odds ratio [OR] 1·50, 95% CI 1·23-1·82) and poorer functional outcomes (modified Rankin scale score 3-6; 1·52, 1·25-1·85) compared with non-carriers after lobar ICH. By contrast, APOE ε4 was not associated with lobar ICH volume, functional outcome, or mortality (56). Several other genetic variants are also associated with CAA and ICH, for example, CR1 (complement component receptor), TGF-β1, and TOMM40 but further work is needed to confirm these. (52) New genetic associations with CAA are sure to emerge from large international collaborative efforts in the coming years.

There is substantial evidence supporting the hypothesis that CAA is an important contributory factor in causing ICH. This association between CAA and ICH was noted as far back as the 1970s and 1980s in a series of pathologically confirmed case reports of ICH (57-61); a large systematic review and meta-analysis of published histopathological studies confirmed an association between CAA and lobar ICH (OR 2.21, 95% CI 1.09 to 4.45) (62). A meta-analysis of prospective studies in ICH cohorts shows patients with CAA related ICH had a much higher annual ICH recurrence rate than patients with non-CAA related ICH (7.4% vs. 1.1% p=0.01)(63). Given the very high pathological prevalence of CAA in population-based studies, and the much lower incidence of CAA related ICH, most patients with CAA pathology do not suffer ICH. Elucidating which patients with CAA will develop CAA related ICH is a key question for preventing CAA-related ICH. A pathological study comparing brains with CAA and ICH to those with CAA without ICH found CAA was more severe in the brains with cerebral haemorrhage than in those without, and that fibrinoid necrosis was only seen in the brains with cerebral haemorrhage [48]. Microaneurysms occurred only in the presence of severe, rather than moderate or mild, CAA (64). This suggests that mild CAA may not confer such a high risk of ICH, and that preventing progression of CAA may thus reduce the incidence of ICH.

2.2 Hypertensive arteriopathy

Hypertensive arteriopathy is a term often used to describe multiple different (non-CAA) pathologies affecting mainly the deep arterial perforators (including arteriolosclerosis, lipohyalinosis, and fibrinoid necrosis) (65-67) some of which are not clearly directly related to hypertension (68, 69). Despite the different pathological findings and aetiologies, it is still generally considered to be one disease. Sporadic SVD is a more encompassing term (68), but this term may also include CAA depending on how a small vessel is defined. The most severe histopathological correlate of hypertensive injury is fibrinoid necrosis, which is more commonly found in brains from hypertensive patients than in those without hypertension (70-72) as well as in arterioles adjacent to deep ICH(71-74). Furthermore, a study from the late 1970s showed marked elevation in blood pressure can produce fibrinoid necrosis acutely (75).

Historically, hypertension has been considered the cause of the majority of non-lobar (i.e. deep) ICH. This observation first arose from autopsy series from the late 50s and early 70s of patients with deep ICH in which classical pathological vessel changes suggested hypertensive arteriopathy. (71, 73). These presumed hypertensive related changes, including microaneurysms (‘Charcot-Bouchard’ or ‘miliary’ aneurysms), occurred in small penetrating arteries and arterioles subjected to high pressures such as the lenticulostriate arteries emanating from the middle cerebral artery, basilar and posterior cerebral artery perforators. These small arteries feed deep central areas of the brain such as the basal ganglia, thalami, and brainstem (24) corresponding to the common locations of deep ICH. Thus, deep ICH has for many years been commonly attributed to hypertension and termed ‘hypertensive haemorrhage’. This theory has been challenged, primarily by the finding of a low prevalence of hypertension in some ICH cohorts (76, 77) as well as pathological studies in which findings previously attributed to hypertension have been observed in the absence of hypertension (78) and associations of deep perforator SVD with other factors (e.g. reduced cerebral perfusion) (68, 79-85). Nevertheless, for simplicity and consistency, in this thesis we will use the term ‘hypertensive arteriopathy’ to include non-CAA SVD affecting the small deep perforating arteries.

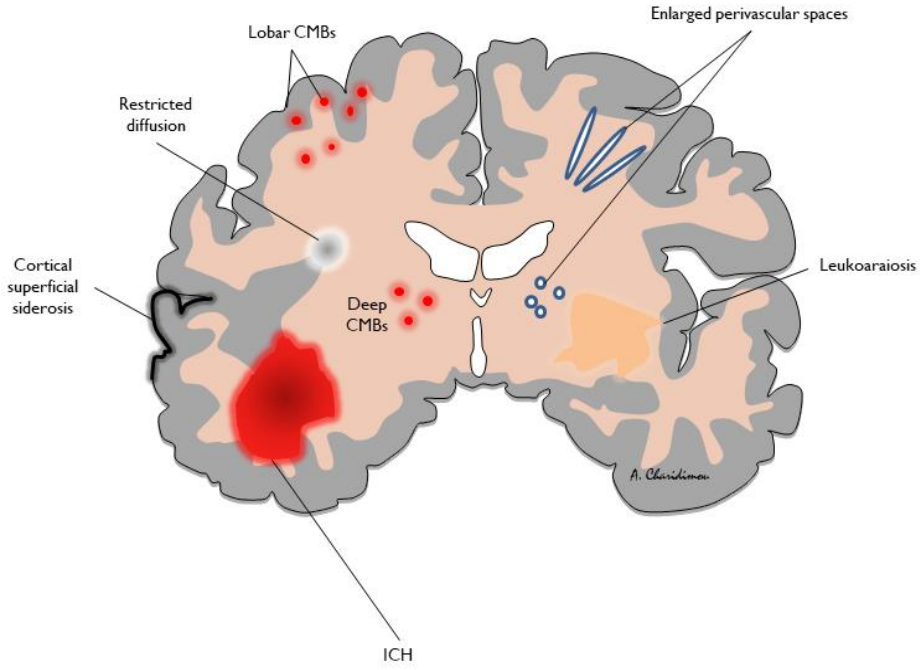
Genetic studies have shown associations with the occurrence and outcome of deep ICH presumed due to hypertensive arteriopathy. A recent study showed a strong association between the size of haemorrhage, clinical outcome and known hypertension risk alleles in those with deep ICH (86). This study demonstrated an increase in hematoma volume by 28% and an increased risk of a poor clinical outcome by 71% for every standard deviation rise in a blood pressure based genetic risk score.

Attributing lobar ICH to CAA and non-lobar ICH to hypertensive arteriopathy, while attractive for clinicians, is clearly an oversimplification. There is evidence from a large systematic review and meta-analysis showing lobar haemorrhages are significantly associated with CAA (62), but there was no statistically significant negative association between CAA and deep ICH. Furthermore, hypertensive arteriopathy can affect the white matter perforators and thus cause a proportion of lobar ICH in addition to deep ICH (87). Importantly older individuals may, in fact, have a mixture of both CAA and hypertensive arteriopathy, as both are age-dependent (33).

2.3 Neuroimaging markers of small vessel disease

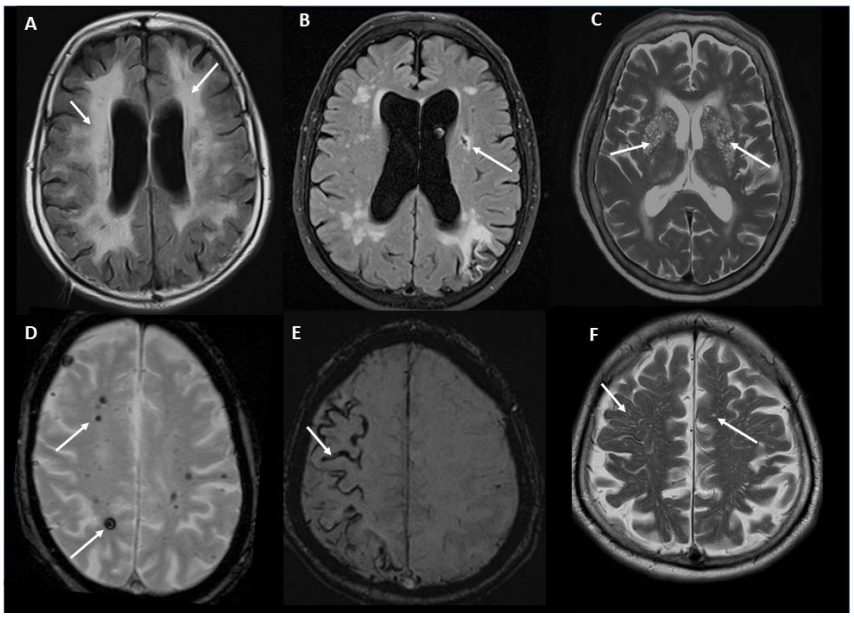
Neuroimaging, particularly with MRI, is the most useful way to visualize the consequences of small vessel disease. Although the small arteries are generally beyond the resolution of MRI, their complex effects on the brain (from both ischaemia and hemorrhagic processes) are clearly seen. Here we consider each neuroimaging marker in terms of its diagnostic and prognostic utility regarding future ICH. I present a schematic illustration of the main MRI markers of the small vessel diseases relevant to ICH in Figure 3 and example MRI images are shown in Figure 4. The focus of the thesis is predominantly on cerebral microbleeds (CMBs), cortical superficial siderosis cSS and white matter hyperintensities (also known as leukoaraiosis), thus most attention will be given to them.

Figure 3 Schematic showing markers of small vessel disease seen on brain imaging



From Wilson et al: Expert Rev Neurother. 2014 Jun;14(6):661-78

Figure 4 MRI imaging example of small vessel disease markers.



A) White matter hyperintensities (white arrows), **B)** Lacunar infarction (white arrow), **C)** Basal ganglia enlarged perivascular spaces, **D)** Cerebral microbleeds, **E)** Cortical superficial siderosis, **F)** Centrum semiovale enlarged perivascular spaces

2.3.1 Cerebral microbleeds

Cerebral microbleeds (CMB) are an imaging marker defined as small homogenous round hypo-intense areas on blood-sensitive T2*-weighted gradient-recalled echo or susceptibility weighted MRI sequences. (88). A histopathological-MRI correlation study confirmed that small clusters of haemosiderin-laden macrophages were the pathological correlate of the majority of microbleeds seen on MRI (89). Further histopathological correlation studies showed that vessels near CMBs are affected by pathological changes of cerebral small vessel disease (89-93). Thus, it is inferred that most CMBs represent direct extravasations of blood from bleeding-prone vessels affected by small vessel diseases. Mechanisms of CMBs development other than direct red cell extravasation have also been postulated, for example, ischaemia-mediated iron store release by oligodendrocytes (94) and phagocytosis of red cell microemboli into the perivascular space (termed angiophagy) (95). A recent pathological analysis of the "oldest old" (over 85 years) found that areas of haemorrhage (including microscopic bleeding) were frequently associated with microinfarcts, (96) suggesting a "secondary" mechanism, perhaps related to haemorrhagic transformation of ischaemic infarcts. Indeed, a now well-cited editorial suggests a possible framework for the classification for CMBs: primary (artery/arteriole rupture or blood-brain barrier dysfunction); secondary (haemorrhagic infarction or microinfarction); and "pseudo" CMBs (angiophagy and ischaemia-related iron store release) (97).

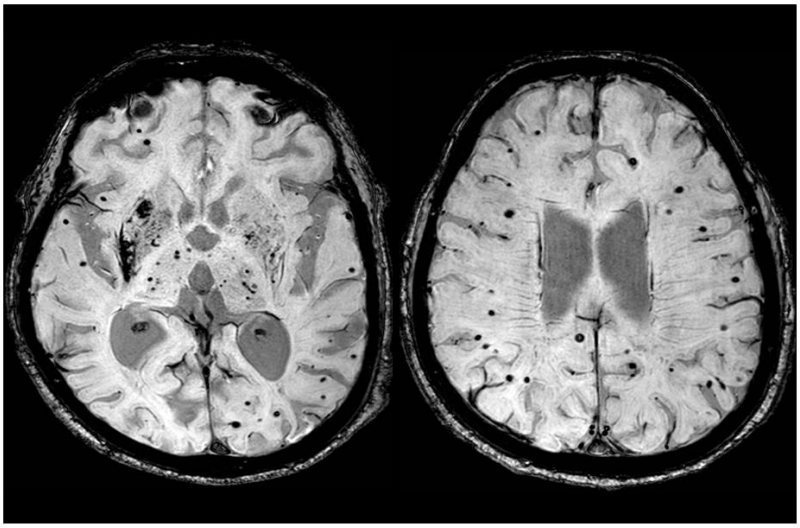
Although studies of the pathological correlates of CMBs are sparse and include only 23 patients (93, 98) mainly with ICH or dementia, most observations suggest that CMBs are self-limiting regions of red cell extravasation from damaged small blood vessels.

2.3.1.1 CMB location and relationship to underlying SVD subtype

The location of CMB may be helpful in determining the underlying SVD aetiology, although much of the evidence for this is indirect. Deep CMB are more commonly associated with putative markers of hypertensive arteriopathy, whilst strictly lobar CMBs (cortical-subcortical) are hypothesized to reflect CAA (Figure 5). (88, 99). This hypothesis is supported by the association between strictly lobar CMB with APOE ε4, a known marker of CAA, initially in a large population-based study (100) and subsequently confirmed in 2 meta-analyses. (101, 102) Molecular imaging studies using PET amyloid ligands suggest that lobar CMBs preferentially occur at site of high amyloid-β concentration (103). By

contrast, deep (basal ganglia and infratentorial) CMBs are related to deep ICHs (104, 105), cardiovascular risk factors, lacunar infarcts and white matter lesions (100) The diagnostic significant of CMBs in a mixed topography requires further study; it is likely that in such cases a mixed pathology exists. Although deep CMBs seem likely to reflect only hypertensive arteriopathy, lobar CMBs may result from an interaction between hypertensive arteriopathy and CAA (87). The Boston criteria used for the diagnosis of CAA related ICH relies on this topographical pattern. The criteria categorize the diagnosis into either definite, probable with supporting evidence, probable, or possible CAA based on the certainty of the diagnosis. The probable CAA group (which is the first criteria which doesn't require pathological tissue) has been validated with high specificity in a clinical-pathologic correlation study (91), potentially obviating the need for further diagnostic work-up and a tissue diagnosis. However, the Boston criteria have been subject to only limited pathological validation, mainly from the single specialist center in Boston. A study in 2001 (91) validated the criteria with the gold standard pathologically proven CAA and found a high specificity but a low sensitivity (44%) likely owing to the low use of T2*-weighted gradient echo MRI in the study. The prevalence of CAA related lobar haemorrhage was high (74%) and thus the validation may not be applicable to patients without ICH. Further validation in amyloidosis-Dutch type patients showed that using T2* weighted gradient echo increased the sensitivity from 48% to 63% (106). More recently a different European study validated the Boston criteria with the addition of T2* against the gold standard (pathologically proven CAA) and found the sensitivity to be 77%.(107) Thus, although the Boston criteria are a key advance and remain highly specific, there is clearly a need for further validation studies in larger cohorts in different populations with routine T2* gradient echo MRI and to explore the contribution of other MRI imaging markers.

Figure 5: Deep and Lobar CMBs

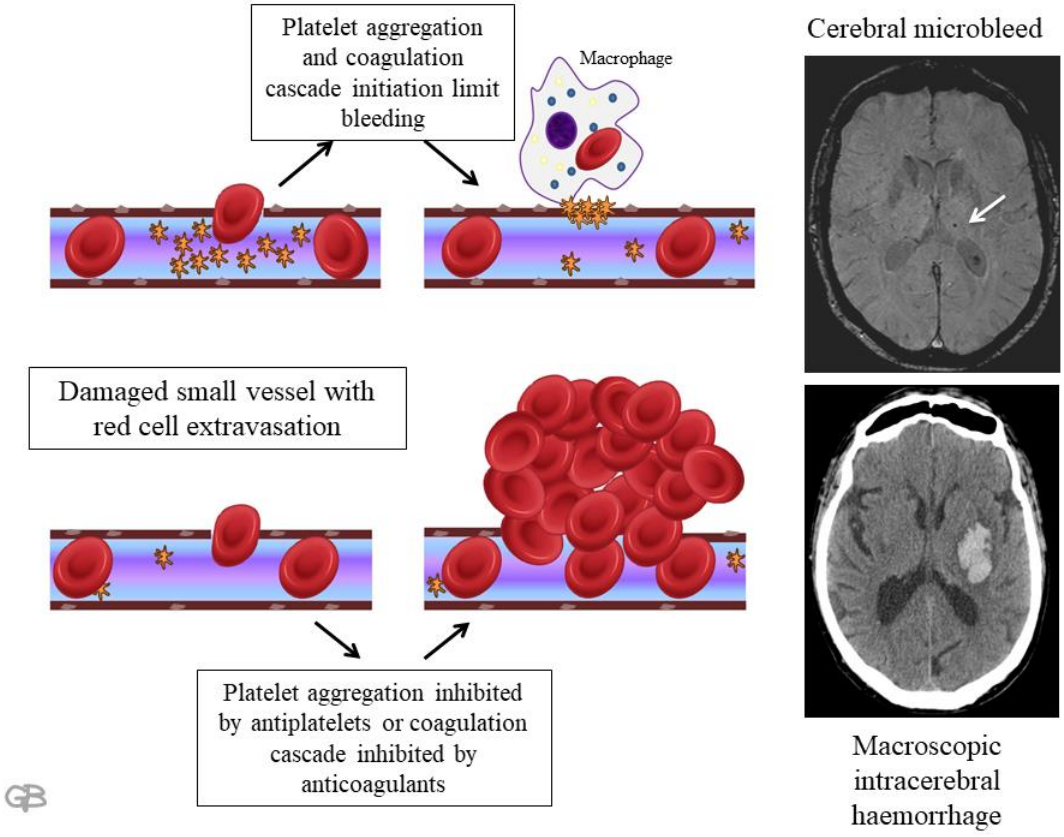


SWI imaging: Left image showing mixed CMB distribution with CMB located in the thalamus, basal ganglia structures, and temporal lobe. Right image showing CMBs located in the lobar regions

2.3.1.2 CMB relationship to antithrombotics and ICH

CMBs might be relevant for ICH risk with antithrombotic exposure: first, CMBs are common in populations likely to be exposed to antithrombotic drugs, including older community-dwelling individuals and those with ischaemic stroke, TIA or ICH (108); and second, longitudinal studies confirm that CMBs develop over time after ischaemic stroke, TIA or ICH (109, 110) (while regression of CMBs can occur, it seems to be rare). Since antithrombotics impair haemostasis by inhibiting platelet aggregation (antiplatelets) or disrupting the coagulation pathway (anticoagulants), in the presence of a CMB-related arteriopathy, self-limiting red blood cell extravasation (causing a CMB) could become a symptomatic ICH (Figure 6).

Figure 6 Schematic hypothesizing how ICH develops from CMBs in presence of anithrombotics



From Wilson et al: Curr Opin Neurol. 2017 Feb;30(1):38-47

Although their radiological definition is established, given the complexity of possible mechanisms underlying CMBs, they may not be associated with the same risks of haemorrhage or ischaemia in all populations.

Non-stroke (older community) populations

The diagnostic accuracy of a strictly lobar CMB pattern for CAA seems limited in non-ICH (community) cohorts: a histopathological study in non-hospital community patients shows strictly lobar CMBs have a positive predictive value for pathology-proven CAA of only 25% (111), though participants had very few CMBs (112). There are several longitudinal studies in community patients exploring the relationship between CMBs and ICH. In the Rotterdam study of 4759 participants aged ≥45 years with mean follow-up of 4.9 years

(108), CMBs were associated with an increased risk of all stroke (HR 1.93; 95% CI 1.25 to 2.99); this was lower for ischaemic stroke (HR 1.52; 95%CI 0.91 to 2.53) than for ICH (HR 5.64; 95% CI 1.66 to 19.53). Non-strictly lobar CMBs (i.e. non-CAA pattern), were associated with an increased the risk of both ischaemic stroke and ICH while strictly lobar CMBs (indicating probable CAA) were associated only with ICH risk. Six participants with multiple CMBs developed a first-ever ICH during follow-up; Three had used antithrombotic agents (either platelet inhibitors or oral anticoagulants). However, the overall stroke risk associated with CMBs was not affected using antithrombotics. Pre-existing CMBs were associated with lacunar infarction whilst new lobar CMBs were associated with progression of white matter lesions, suggesting shared ischaemic mechanisms.

A large Japanese population-based study showed that CMB presence was associated with both ischaemic stroke (hazard ratio 4.48; 95 % CI 2.20 to 12.2) and ICH (hazard ratio 50.2; 95 % CI 16.7 to 150.9)(113), but did not explore CMB burden, topography, or associations with antithrombotics. A hospital-based study in patients with incidental lobar CMBs without stroke reported ICH rates comparable to CAA-associated ICH (114) and that warfarin was an independent risk factor for ICH (p=0.02). However, this population had a median of 10 lobar CMBs, suggesting a severe microangiopathy, so these findings cannot be generalised to other stroke-free populations with incidentally found CMBs.

In summary, in community-dwelling populations, there is no clear evidence that the benefits of ischaemic stroke prevention using antithrombotic drugs outweigh the risk of ICH in people with CMBs. Further interventional controlled clinical trials, including stratification according to CMB presence, burden and distribution, will be needed to definitively answer this question.

Ischaemic stroke and TIA populations

The clinical relevance of CMBs is perhaps most uncertain in the ischaemic stroke and TIA population because standard care includes antithrombotics for stroke secondary prevention. Does any increased risk of ICH in patients with CMBs outweigh the benefit in reduced

future ischaemic stroke risk associated with antithrombotic therapy? Although risk instruments can be used to assess overall future ischaemic stroke risk in AF (e.g. CHA_2DS_2VASC) or after TIA (ABCD2), as well as overall bleeding risk in AF (e.g. HAS-BLED), there are currently very limited data on how CMBs and other brain neuroimaging findings might help personalise antithrombotic therapy to maximize benefit and minimize risk.

In recent studies, antiplatelets (115-117) and anticoagulants (117, 118) are associated with the presence of CMBs and the development of new CMBs over time. However, establishing the clinical relevance of CMBs requires key clinical outcomes, including recurrent stroke.

An aggregate data meta-analysis of 10 published prospective studies of ischaemic stroke / TIA cohorts found that CMBs are associated with both new ICH (OR 8.52; 95% CI4.23 to 17.18) and recurrent ischaemic stroke (OR 1.55, 95% CI 1.12 to 2.13) although this was based upon very few ICH events and risk stratification by ICH burden and distribution was not possible(119).

Data on the association between CMBs and stroke risk in patients with ischaemic stroke or TIA treated with anticoagulants are extremely limited. A small study in 134 patients with TIA or ischaemic stroke associated with AF (65% treated with anticoagulants) over a median follow-up of 2.4 years (120), found that CMBs were associated with an increased unadjusted risk of all stroke (21% vs 9%, $p = 0.06$) but there was only 1 ICH. A study from Korea in 504 patients with ischaemic stroke or TIA (97% discharged on anticoagulation) (121) found that strictly lobar CMBs were associated with ICH mortality (HR 5.91; 95% CI 1.58 to 22.11) whilst increasing CMB burden was associated with all-cause mortality (HR 1.99; 95% CI 1.03 to 3.85) and ischaemic stroke mortality (HR 3.39; 95% CI 1.39 to 8.28) but did not report on non-fatal ischaemic stroke or ICH. A retrospective study from the same Korean group including 550 ischaemic stroke patients with AF (83% discharged on anticoagulation) found that higher CHADS2 and CHA(2)DS(2)VASC scores were associated with the presence and number of CMBs. Recurrent ICH was associated with CMB presence (HR 3.79; 95 % CI 1.09 to 13.15) but not CHADS2 or CHA(2)DS(2)VASC scores; recurrent ischaemic stroke risk was not reported (122). A small prospective single

centre study from Japan followed 119 patients with AF (86% anticoagulated) for a median of 17 months (123); CMBs were not associated with recurrent stroke (both ICH and ischaemic stroke), but due to the small number of events ischaemic stroke and ICH risk could not be examined separately.

ICH populations

Recurrent ICH risk varies according to the location of the initial ICH: the annual ICH recurrence risk after deep (non-lobar, in the basal ganglia or brainstem) ICH is between 1.3 to 10.6% compared with 2.5 to 28.2% after lobar ICH (3). While deep ICH is attributed to hypertensive arteriopathy, lobar ICH may be due to either hypertensive arteriopathy or CAA. Cohort studies in CAA-related ICH, diagnosed according to the Boston criteria indicate a high recurrence rate of ~10% per year (114). The presence, burden, and distribution of CMBs might increase the risk of recurrent ICH and help to judge difficult antithrombotic decisions. In a study of 207 survivors of ICH followed for a median of 20 months, there were 39 recurrences of ICH (124). CMB number was associated with recurrent ICH in patients with lobar but not deep ICH, while antiplatelet use did not affect the risk of recurrent ICH in either lobar (HR 0.8; 95% CI 0.3 to 2.3, $p = 0.73$) or deep location (HR 1.2; 95% CI 0.1 to 14.3, $p = 0.88$). By contrast, a small single centre study in CAA-related ICH reported that aspirin was an independent risk factor for recurrent ICH (HR 3.95; 95% CI 1.6 to 8.3, $p = 0.021$) (125).

Three other studies found that increasing CMB burden is associated with increasing ICH risk (125-127), but none reported on ischaemic stroke risk. Two of these studies included only patients with lobar ICH, whilst the third included both deep and lobar ICH. The risk of ICH was particularly high with >5CMBs (HR 4.12 95% CI 1.6 to 9.3 vs. no CMBs $p = 0.001$ (125) with a 51% three-year cumulative risk for >5 CMBs vs. 14% three-year cumulative risk for 1 CMB p = 0.003(126). A meta-analysis of 10 studies in ICH cohorts with prospective data shows in patients with CAA, having multiple microbleeds increased your risk of ICH, although there was not a clear increase in risk with increasing microbleed burden (63). Whereas in non-CAA related ICH patients, only >10 CMBs was significantly associated with a higher risk of ICH recurrence when compared to patients without CMBs.

The use of anticoagulants following ICH thus presents a major clinical dilemma. The risk of ischaemic stroke without antithrombotic treatment must be weighed carefully against the possible increase in ICH risk associated with antithrombotic therapy. A decision analysis which modelled on survivors with ICH and AF suggested that in lobar ICH avoiding warfarin increased quality-adjusted life years by 1.9, compared with 0.3 for deep ICH; the authors concluded that anticoagulation for AF should not be offered to patients with lobar ICH and only to survivors of deep ICH if the risk of ischaemic events was high (>7% per year) (128). However, CMBs were not considered in this analysis. By contrast, recent real-world studies in large datasets from ICH survivors with AF suggest that anticoagulation reduces mortality and ischaemic complications, without an increase in ICH (129, 130), and reduced hospitalization costs (131). However, none of the real-world studies stratified ICH by location, nor by SVD burden or distribution. Further studies in ICH cohorts phenotyped according to CAA diagnostic criteria, with an assessment of interactions of CMB pattern and burden with antithrombotic use may help clarify this enduring clinical dilemma. Ongoing randomised trials of antithrombotic use after ICH will also help guide clinicians in these decisions in future: these include RESTART (ISRCTN71907627), SoSTART (NCT03153150), RESTART-FR (NCT02966119), STATICH (NCT03186729), NASPAF-ICH (NCT02998905), A3-ICH (NCT03243175), APACHE-AF (NCT02565693).

Table 2: Ongoing RCTs investigating antithrombotic use in ICH populations

Study name	Population	Antithrombotic Medication
RESTART	Adults surviving spontaneous intracerebral haemorrhage who had taken an antithrombotic drug	Antithrombotics or anticoagulants vs. No antithrombotics
SoSTART	Adults surviving spontaneous symptomatic intracranial haemorrhage with persistent/paroxysmal atrial fibrillation/flutter	Anticoagulants vs. No antithrombotics
RESTART-FR	Adults surviving spontaneous intracerebral haemorrhage who had taken an antithrombotic drug	Antithrombotics or anticoagulants vs. No antithrombotics
STATICH	Adults surviving spontaneous intracerebral haemorrhage who had taken an antithrombotic drug	Antithrombotics or anticoagulants vs. No antithrombotics
NASPAF-ICH	Adults surviving spontaneous symptomatic intracranial haemorrhage with persistent/paroxysmal atrial fibrillation/flutter at high risk of infarction	NOACs vs. Aspirin
A3-ICH	Adults surviving spontaneous symptomatic intracranial haemorrhage with persistent/paroxysmal atrial fibrillation/flutter	Apixaban vs. Left atrial appendage occlusion vs. No antithrombotics
APACHE-AF	Adults surviving spontaneous symptomatic intracranial haemorrhage with persistent/paroxysmal atrial fibrillation/flutter	Apixaban vs. Antiplatelets vs. No anthithrombotics

2.3.2 Cortical Superficial Siderosis (cSS)

Cortical superficial siderosis (SS) is a condition in which haemosiderin is deposited on the pial surfaces of the brain and restricted to the supratentorial cerebral hemispheres (132). This is a distinct clinical entity, different from infratentorial superficial siderosis of the CNS(133)

2.3.2.1 Relationship to underlying arteriopathy

Cortical SS (cSS) is now recognized as a characteristic neuroimaging manifestation of CAA (134-136). It is presumed to be due to rupture of the small vessels very close to the cerebral convexities resulting in convexity subarachnoid haemorrhage (137, 138) followed by subsequent haemosiderin formation and deposition. Convexity subarachnoid haemorrhage has a high incidence of subsequent ICH, especially in those with a diagnosis of CAA (139). The true prevalence of cSS in patients with CAA is not well known: recent studies reported rates of 40% and 60% (136, 137) in clinical-radiological cases and histopathological-proven cases of CAA respectively. cSS in patients without CAA seems to be rare; no cases were identified in the histopathological-proven non-CAA ICH control group in the study above (137) and only in 0.7-0.9% of normal elderly subjects (140, 141)

2.3.2.2 Relationship to ICH

cSS and its most common cause, convexity subarachnoid haemorrhage, are both associated with transient focal neurological episodes (TFNE) sometimes referred to as “amyloid spells” (142). In a retrospective cohort of patients with TFNEs, after an average time of 14 months, 50% (12/24) of this group went on to have a lobar ICH (143).

Three published studies (144-146) show high occurrences of subsequent recurrent ICH in those found to have cSS. The first of these studies reported a subsequent haemorrhage rate of just under 50%, the majority of these being intracerebral (144). There was no difference between those with focal cSS and disseminated cSS. There was, however, no non-cSS control group. A study including a control group shows the ICH rate at 4 years was 25% (95%CI: 7.6-28.3%) for patients without siderosis; 28.9% (95%CI: 7.7-76.7%) for patients with focal siderosis; and 74% (95%CI: 44.1-95.7) for patients with disseminated cSS (affecting more than 3 noncontiguous sulci). The hazard ratio of any cSS corresponded to

an increased risk of 2.5 times, whilst disseminated cSS amounted to 3 times the risk when compared to those without cSS (145). In addition to cSS having a high recurrence rate of ICH, a small study from Boston shows cSS is a predictor of early ICH recurrence (defined as within 6 months of index event)(146). A new cSS score assessing cSS multifocality shows the risk of ICH increases as the degree of multifocality increases (as high as 26% per annum with a score of four, suggesting ICH risk increases with increasing disease severity (147). Furthermore, a pooled analysis of patients with convexity subarachnoid haemorrhage (the most common cause of cSS) who had suspected CAA, the incidence of subsequent ICH was 16% per patient-year and as high as 19% per patient-year in those with 'probable CAA' as diagnosed using the Boston criteria (139). Lastly, in patients with CAA and cSS without a history of ICH, the rate of ICH at 5 years is 19% suggesting cSS is also a marker of future ICH risk even in patients without ICH (148). These results suggest that cSS (and convexity subarachnoid haemorrhage) may be a powerful neuroimaging marker to predict recurrent ICH in CAA with implications for antithrombotic and preventive treatments.

2.3.3 White matter hyperintensities of presumed vascular origin (leukoaraiosis)

Leukoaraiosis (leuko = white, araisosis = rarefaction) is a broad term originally used to describe confluent areas of low density on CT scans (149), but subsequently applied to high signal areas on T2-weighted MRI scans. More recently these changes on T2 and FLAIR MRI have been termed "White matter hyperintensities of presumed vascular origin" (WMH) (11). I will use these terms interchangeably throughout this thesis, largely depending on the neuroimaging modality. WMH have a heterogeneous pathological substrate and can arise from many different mechanisms (150) but are mostly thought to be due to changes in cerebral microangiopathy, however, damage to the blood-brain barrier is another hypothetical cause(151). Thus, WMH is a non-specific marker of SVD damage.

2.3.3.1 Location of WMH and relation to underlying SVD subtype

WMH can be caused by both hypertensive arteriopathy and CAA, whilst it is hypothesized that posterior leukoaraiosis was more likely to reflect CAA (as CAA has a predilection for the parieto-occipital lobes (152-154)), two separate studies have shown that the distribution of WMH is similar among differing pathologies in ICH patients, (155, 156) suggesting

topography of leukoaraiosis may therefore not be a very useful marker of the underlying SVD. Whilst white matter hyperintensity location alone may not be helpful in identifying the predominant underlying microangiopathy the shape, size and pattern may help differentiate subtypes (157) although this needs to be validated in larger and representative cohorts

2.3.3.2 Relationship to ICH

Whilst there is considerable evidence linking leukoaraiosis to post-thrombolysis haemorrhage (158), the evidence in stroke patients not thrombolysed is less compelling. Prospective studies in patients with ischaemic stroke show conflicting results: two observational studies(122, 123) failed to show any statistically significant relationship between WMH and ICH incidence whilst one randomized control trial (RCT) in patients with ischaemic stroke presumed to be arterial in origin, did find an association (hazard ratio 2.7, 95% confidence interval 1.4 to 5.3). In patients with ICH the evidence is limited to one longitudinal study (159) in patients with lobar ICH: The hazard for recurrent lobar ICH was 4 times higher for patients with WMH compared to those without after controlling for APOE genotype and history of previous ICH, although there was not a dose-related response. This is also the only study in either cohort to show leukoaraiosis is an independent risk factor for ICH in those not on any form of antithrombotic drugs (159).

2.3.4 Other common neuroimaging markers of small vessel disease (not explored further in thesis)

2.3.4.1 Diffusion weighted imaging hyperintense lesions (DWIHL)

The finding of diffusion-weighted imaging hyperintensities remote from the hematoma after or during the acute to the sub-acute stage of ICH is a relatively new finding, as such there has been no standardization in nomenclature. In the literature, they have been referred to as "acute ischaemic brain lesions", (160) "ICH associated diffusion-weighted lesions" (161) "new ischaemic lesions in setting coexisting with ICH" (162) and "silent ischaemic lesions" (163). Conversely, diffusion-weighted imaging hyperintense lesions have been suggested in some cases to represent haemorrhages (164)

The prevalence of these lesions ranges from 13% (160) to as high as 35% (163), there is a strong correlation with leukoaraiosis (160, 165) and CMBs (160, 162, 163) as well as aggressive lowering in blood pressure in the acute setting of ICH.

Their diagnostic and prognostic value remains undetermined until further studies are undertaken. They do however add to the hypothesis that SVD is likely to be a major contributory factor in cases of spontaneous ICH

2.3.4.2 MRI-visible perivascular spaces

Perivascular spaces are interstitial fluid-filled cavities surrounding small penetrating arterioles, which form important drainage pathways allowing interstitial fluid and solute efflux from the brain. (166-169). Inflammatory processes and SVD are thought to damage the blood brain-barrier and disrupt these spaces and drainage pathways. Limited histopathological correlation studies show arterial wall thickening and tortuosity, venular widening, features of inflammation and blood-brain barrier failure adjacent to these enlarges spaces. (170) MRI-visible perivascular spaces (PVS) have long been considered a 'normal' age-related or incidental finding, but emerging evidence suggests that they may be another marker of underlying SVD presence, severity or subtype.

Whilst PVS and their association with ischaemic and lacunar stroke have been well documented (171-173) there has been little interest in their association with ICH. A recent

paper has shown an association between CAA-related lobar ICH with severe cerebral white matter (i.e. centrum semiovale) PVS and deep ICH with severe basal ganglia PVS (174). These findings support the hypothesis that CAA might be mechanistically associated with centrum semiovale PVS and hypertensive arteriopathy with basal ganglia PVS.

Further studies are needed to investigate PVS as a biomarker of SVD (93, 175-177) and their location as a possible indicator of the specific underlying type of SVD. A key question is whether PVS increase the sensitivity of MRI in detecting CAA, and whether they provide an earlier neuroimaging marker for the diagnosis of CAA.

2.3.4.3 Cerebral microinfarction (CMI)

CMIs are small presumed ischaemic lesions (100 μm to 5mm) naked to macroscopic examination on pathological evaluation. They are a common finding in cerebrovascular patients, especially those with CAA (178, 179). Initially considered to be invisible on in-vivo imaging(178), recently high resolution structural MRI(180) and diffusion weighted imaging (181) has allowed identification of the largest CMIs without the need for tissue.

CMIs have a strong association with SVD and their distribution could help define SVD subtypes; a large pathological study showing CMIs cortical CMIs were associated with CAA, whereas subcortical CMIs were associated with arteriolarsclerosis (182). A smaller study suggests occipital CMIs are associated with CAA, whereas frontal CMIs were not (183). Despite this, CMIs should not be thought of as specific to SVD as both large vessel disease (184, 185) and cardiac disease(186) also have strong associations with CMIs.

In stroke populations CMIs have been associated with cognitive dysfunction at two years (187), furthermore the predicted annual incidence of CMI is thought to be higher in ICH populations vs. non-ICH populations(181) but little is known regarding subsequent ischaemic stroke or ICH.

3.0 Summary and thesis aims

Advances in neuroimaging have allowed a greater understanding of small vessel disease and its relation to the underlying pathogenesis of ICH. Indeed, CMBs and cSS are now part of small vessel disease classification.

Despite these advances, there are many important unanswered clinical questions, including the following:

- **Are the rate and risk of ICH or recurrent ischaemic stroke predicted by neuroimaging markers of small vessel disease in patients with ischaemic stroke or TIA?**

  The risk of ICH associated with CMBs has largely been derived from patients with ICH, with only a few prospective studies in patients with ischaemic stroke. We do not know whether the burden or distribution of CMBs has any relation to ICH risk in these cohorts. This gap in scientific knowledge coupled with the more widespread identification of these markers in patients with ischaemic stroke has led to clinical uncertainty, particularly regarding the use of antithrombotics (antiplatelet and anticoagulant drugs) in these patients.

- **Can positive identification of small vessel disease provide diagnostic utility in identifying 'primary ICH'?**

  Primary ICH by its very definition is presumed to be caused by small vessel disease yet current diagnostic algorithms fail to utilize neuroimaging correlates of small vessel disease.

- **Does recurrent stroke risk differ by ICH location or SVD markers in patients with ICH?**

  ICH location and markers of small vessel disease reflect differing SVD subtypes; these markers may therefore, help predict future ICH and ischaemic stroke risk.

3.1 Main objective of the thesis

Based on these gaps in knowledge, the overall objective of this thesis is to explore whether neuroimaging of ICH and neuroimaging markers of small vessel disease can; (1) aid with the diagnosis of stroke due to ICH; and (2) improve the risk prediction of subsequent strokes in patients with ischaemic stroke, TIA, and ICH. I accomplish this by reviewing the prevalence, clinical associations, and outcomes associated with markers of small vessel disease in different stroke populations: (1) ischaemic stroke and TIA populations; and (2) ICH populations.

3.2 Ischaemic stroke populations

In chapter 4 I provide a definitive synthesis of current evidence regarding CMB presence, burden, and distribution with stroke risk (both ischaemic and haemorrhagic) in patients with ischaemic stroke by undertaking a systematic review and meta-analysis. In chapter 5 I describe a large observational cohort (CROMIS-2) to explore whether CMBs, cSS and white matter hyperintensities are independent risk factors for intracerebral haemorrhage in patients with cardioembolic stroke who have been started on anticoagulation. I then describe the development of new risk prediction scores for ICH with the addition of CMBs and compare these to existing clinical risk scores.

3.2 Intracerebral haemorrhage populations

In chapter 6 I explore how the identification of small vessel disease helps differentiate so-called ‘primary ICH’ from ‘secondary ICH’ and how this may tailor subsequent investigations. In chapter 7 I investigate associations between recurrent ICH and new ischaemic stroke in an ICH population with attention to markers of small vessel disease and ICH location. In chapter 8 I explore whether the ischaemic stroke risk prediction score (CHA_2DS_2VASC) is useful in an ICH population and whether this can be improved with the addition of markers of small vessel disease.

PART 2

ISCHAEMIC STROKE POPULATIONS

4.0. How does presence, burden and distribution of cerebral microbleeds contribute to recurrent stroke risk?

Objectives: To determine associations between cerebral microbleed (CMB) burden with recurrent ischaemic stroke and intracerebral haemorrhage (ICH) risk after ischaemic stroke or TIA.

Methods: We identified prospective studies of patients with ischaemic stroke or TIA which investigated CMBs and stroke (ICH and ischaemic stroke) risk during ≥ 3 months follow-up. Authors provided aggregate summary-level data on stroke outcomes, with CMBs categorised according to burden (single, 2-4, and ≥5 CMBs) and distribution. We calculated absolute event rates and pooled risk ratios (RR) using random-effects meta-analysis.

Results: We included 5068 patients from 15 studies. There were 115/1284 (9.6%) recurrent ischaemic stroke events in patients with CMBs vs. 212/3781 (5.6%) in patients without CMBs (pooled RR 1.8 for CMBs vs. no CMBs; 95% CI 1.4 to 2.5) There were 49/1142 (4.3%) ICH events in those with CMBs vs. 17/2912 (0.58%) in those without CMBs (Pooled RR 6.3 for CMBs vs. no CMBs; 95% CI 3.5 to 11.4) Increasing CMB burden increased the risk of ischaemic stroke (pooled RR (95% CI): 1.8 (1.0-3.1), 2.4 (1.3-4.4), and 2.7 (1.5-4.9), for 1 CMB, 2-4 CMBs, and ≥5 CMBs, respectively) and ICH (pooled RR (95% CI): 4.6 (1.9-10.7), 5.6 (2.4-13.3) and 14.1 (6.9-29.0) for 1 CMB, 2-4 CMBs and ≥5 CMBs, respectively).

Conclusion: CMBs are associated with increased stroke risk after ischaemic stroke or TIA. With increasing CMB burden (compared to no CMBs), the risk of ICH increases more steeply than that of ischaemic stroke. However, ischaemic stroke absolute event rates remain higher than ICH absolute event rates in all CMB burden categories

4.1 Rationale for study

Cerebral microbleeds (CMBs) are radiologically-defined small round or ovoid regions of signal loss seen on paramagnetic MRI sequences (88). In the limited available pathological correlation studies, CMBs mostly correspond to haemosiderin-laden macrophages close to vessels affected by small vessel disease (SVD) (89-91, 93). It is thus inferred that CMBs are a marker of direct extravasation of red blood cells from arterioles and capillaries damaged by bleeding-prone arteriopathies. An arteriopathy associated with systemic arterial hypertension and pathological changes in small perforating arteries of the deep grey and white matter causes CMBs in deep (basal ganglia) as well as lobar regions. In Western (Caucasian) people with ICH, CMBs in a strictly lobar distribution are highly specific for cerebral amyloid angiopathy (CAA), which causes progressive deposition of amyloid-β in small cortical and leptomeningeal arterial walls (99), though this pattern may not be so specific in Eastern (Asian) people(188) and in those without ICH (111)

Multiple prospective studies in ischaemic stroke cohorts have shown that CMBs are associated with subsequent intracerebral haemorrhage (ICH) risk (46, 48). However, CMBs are also associated with increased subsequent ischaemic stroke risk (189-192). Indeed, suggested ischaemic mechanisms for CMBs include ischaemia-mediated iron store release by oligodendrocytes (94), phagocytosis of red cell microemboli into the perivascular space (termed angiophagy) (95), or hemorrhagic transformation of small “microinfarcts” (96). Indeed, in a recent community study, after adjusting for cardiovascular risk factors, CMBs were found to be associated with lacunes and white matter volume progression (193). Few data are available on how CMB burden affects the balance of ICH and ischaemic stroke risk in different populations. In CAA cohorts, an increasing number of CMBs is associated with an increased risk of ICH, suggesting a relationship between CMB number and the severity of bleeding-prone arteriopathy (126). Whether an increasing number of CMBs is also associated with an increased risk of ICH in ischaemic stroke and transient ischaemic attack (TIA) cohorts remains uncertain. If increasing CMB burden shifts the balance of risk toward ICH rather than ischaemic stroke, this could have major clinical relevance for antithrombotic risk-benefit decisions after ischaemic stroke and TIA. Our previous meta-analysis of 10 prospective studies including 3067 patients with ischaemic stroke or TIA

found that CMB presence is associated with a higher risk of ICH than ischaemic stroke(119) (the odds ratio was 8.53 for ICH and 1.55 for ischaemic stroke), but was not able to address the key clinical question of how the number (burden) of CMBs influences ICH and ischaemic stroke risk.

We therefore performed a pooled analysis of aggregate summary data, including CMB burden and distribution, to investigate the risk of subsequent ischaemic stroke and ICH in individuals who have had an ischaemic stroke or TIA. We tested the following hypotheses: (1) CMB presence is associated with an increased risk of stroke (ICH>ischaemic stroke); and (2) as CMB burden increases (due to a more severe bleeding-prone arteriopathy) the risk of ICH increases more steeply than the risk of ischaemic stroke.

4.2 Methods

We searched Medline and Embase from 1996 (the year CMBs were first reported) through to the April 2015. Our search strategy was:

1) "Cerebral Microbleed*" OR CMB OR "cerebral microh?emorr*" OR "brain microbleed*" OR "Brain microh?emorr*"
2) Stroke OR "Isch?emic stroke" OR TIA OR "Intrac* adj2 h?emorrhag*" OR ICH
3) 1 AND 2

We included published and unpublished studies fulfilling the following criteria: (1) performed paramagnetic-sensitive MRI sequences to detect CMBs at baseline; (2) assessed CMBs at baseline and associations with ischaemic stroke or ICH as primary or secondary outcomes; (3) had a prospective study design with at least 3 months of follow up; and (4) fulfilled at least 4 of 6 pre-defined quality indicators. We excluded cross sectional studies and case series. Two clinical research fellows (AC and DW) reviewed each study for eligibility.

4.2.1 Data extraction:

We contacted all authors to provide data on study population, size, patient year follow up, and antithrombotic treatment. We obtained data on outcome events of symptomatic ischaemic stroke and ICH, with baseline CMB number categories as follows; CMB present; 1 CMB; >1 CMBs; 2-4 CMBs; 5-10 CMBs, >10CMBs, strictly deep CMBs, strictly lobar CMBs and mixed distribution CMBs. We extracted all demographic, imaging, and follow-up outcome data from each study.

All included studies were critically appraised against a checklist of 6 key quality indicators, with reference to the STROBE statement and the PRISMA guidelines. The quality criteria included assessment for bias, and all studies had a quality score of ≥4/6.

4.2.2 Statistical Methods

We first performed separate random effect meta-analyses to derive summary estimates of the pooled risk ratios of ICH and ischaemic stroke for each CMBs category vs. the reference category of "no CMBs". Due to the small number of events in some studies, the

categories 5-10 and >10 were combined, in line with previous studies of CMB burden and prognosis, which demonstrated their prognostic relevance for future ICH risk (126). Logistic regression was then used to estimate the increased risk (odds) of ischaemic stroke/ICH for each additional CMB. First, CMB categories were converted to a continuous scale by assuming that patients in the CMB group's 0, 1, 2-4, 5-10, and >10 had, on average, 0, 1, 3, 7.5, and 12.5 CMBs respectively. Then, for each study, a logistic regression model was fitted relating the (log) odds of ischaemic stroke or ICH to the (estimated) number of CMBs. These (log) odds ratios were then pooled using random effects meta-analysis.

We calculated the I^2 statistic to investigate heterogeneity. Funnel plots (Begg and Mazumdar) were generated to investigate publication bias. Finally, where necessary we undertook meta-regression of confounding covariates of biological plausibility or with differences between the studies (average follow up, age, hypertension prevalence, demographics, antithrombotic use). All analyses were performed using STATA 12.0 (StataCorp LP, TX).

4.2.3 Ethics

Individual studies and data transfer protocols were approved by local Ethics Committees. No additional ethical approval was required for this meta-analysis.

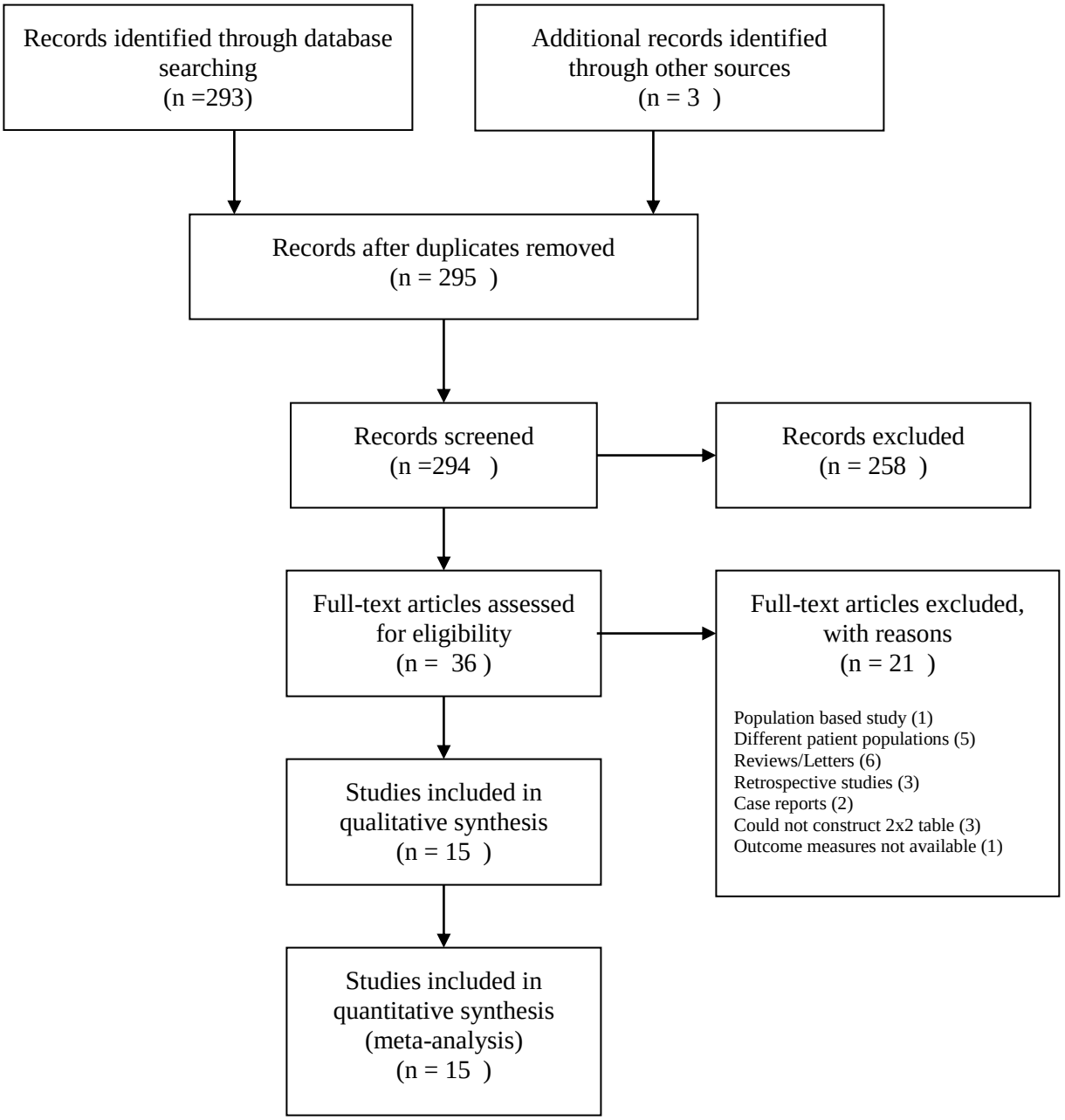
4.3 Results

15 studies met our inclusion criteria (12 published and 3 unpublished) including 5068 patients (46, 122, 189-192, 194-199). Figure 7. The patient and data characteristics of each study are shown in table 3. 12 of the 15 studies provided data on CMBs at the time of the initial ischaemic stroke/TIA fully stratified into number categories and location. 8 studies involving 3111 of patients were from predominantly Eastern (Asian) cohorts; the remainder (1957 patients) were predominantly Western (Caucasian). Two studies included strictly TIA patients, 4 included those with TIA or ischaemic stroke, and 9 included strictly ischaemic stroke patients. The number of patients with CMBs was 1284, giving an overall pooled prevalence of 25.3%. Median follow up was 18 months (IQR 11 to 30). Overall, seventy-nine percent of patients were prescribed antiplatelet agents; only 15% of patients were prescribed anticoagulants (mainly from one study with a high proportion of patients on anticoagulation (87%)) (122). CMB presence was more prevalent, with higher burden in the Eastern cohorts compared to Western cohorts.

Table 3 Patient characteristics of studies included

Study	Patient number	Average follow up (months)	Ethnicity	Cohort	Mean Age	HTN (%)	Gender (% Male)	Antiplatlets (%)	OAC(%)	Tesla	Echo time (ms)	T2*/SWI
Huang	636	14	Eastern	IS	60	67	68	100	0	1.5	NA	T2*
Imaizumi	138	22	Eastern	IS	66	73.2	66	33	2	1.5	26	T2*
Naka	183	18	Eastern	IS	67	70	63	93	2	1	26	T2*
Song	550	30	Eastern	IS	70	77	59	35	87	3	16	T2*
Soo	908	11	Eastern	IS	68	68	58	93	3	1.5	30	T2*
Fan	121	27	Eastern	IS	68	69	68	80	6	1.5	30	T2*
Mok	75	60	Eastern	IS	71	85	52	96	0	1.5	NA	T2*
Kwa	397	46	Western	IS	65	55	59	90	10	1.5	27.6	T2*
Fluri	176	3	Western	TIA	71	72	61	77	12	1.5	15	T2*
Thijs	487	20	Western	IS/TIA	72	64	61	73	27	1.5/3	Variable	T2*
Veltkamp	265	12	Western	IS	65	80	67	78	20	3	19.7	SWI
OXVASC	323	35	Western	IS/TIA	72	63	75	83	11	1.5	14	T2*
Boulanger	236	18	Western	IS/TIA	NA	60	55	NA	NA	3	20	T2*
Lim	500	3	Eastern	TIA	65	66	58	91	15	NA	15-25	T2*
CROMIS-1	68	24	Western	IS/TIA	66	60	66	81	16	1.5	Variable	T2*

Figure 7 Flow Diagram for inclusion into meta-analysis



Part 2: Ischaemic stroke populations

CMBs and ischaemic stroke (ischaemic stroke) risk.

The total recurrent ischaemic stroke rate was 327/5068 (6.5%). The ischaemic stroke event rate in those with CMBs was 9% (115/1284) vs. 5.6% (212/3781) for those without CMBs; thus, CMBs confer an absolute risk increase of 3.4% for ischaemic stroke. The absolute risk increase for ischaemic stroke for CMBs vs. no CMBs, increases as the CMB burden increases (1.8% for 1 CMB, 4.8% for 2-4 CMBs and 5.1% for ≥5 CMBs (table 4).

Table 4 Pooled relative risk for recurrent ischaemic stroke and intracerebral haemorrhage for different CMB burden and distribution (all risk ratios are compared to the reference category of "No CMBs")

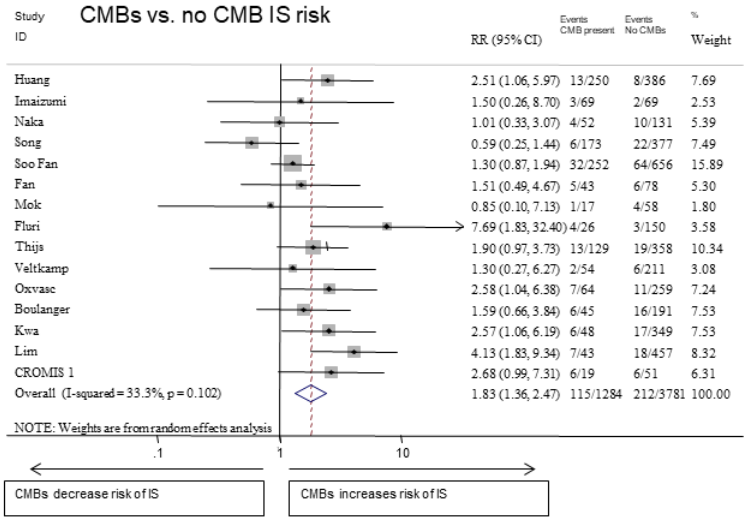
CMB distribution / number	Ischaemic stroke					Intracerebral haemorrhage				
	Pooled absolute event rates n/N (%)	Pooled absolute risk increase %	Pooled RR	Lower 95% CI	Upper 95% CI	Pooled absolute event rates n/N (%)	Pooled absolute risk increase	Pooled RR	Lower 95% CI	Upper 95% CI
CMB presence	115/1284 (9)	3.4	1.8	1.4	2.5	49/1142 (4.3)	3.8	6.3	3.5	11.4
1 CMB	31/433 (7.2)	1.8	1.8	1.0	3.1	8/354 (2.3)	1.7	4.6	1.9	10.7
2 to 4 CMBs	44/433 (10.2)	4.8	2.4	1.3	4.4	9/383 (2.3)	1.8	5.6	2.4	13.3
≥ 5 CMBs	34/342 (10.5)	5.1	2.7	1.5	4.9	24/274 (8.8)	8.2	14.1	6.9	29.0
Strictly lobar	31/332 (9.3)	3.9	2.0	1.4	2.9	12/332 (3.6)	3.2	10.5	4.5	24.3
Strictly Deep	29/437 (6.6)	1.2	1.6	1.0	2.7	6/437 (1.4)	1	3.3	1.3	8.5
Mixed	44/411 (10.7)	5.3	2.6	1.5	4.3	25/411 (6.1)	5.7	11.1	5.5	22.6

n=number of events in each subgroup. N=total number of patients in each subgroup.

Part 2: Ischaemic stroke populations

The risk ratios for different CMB burden and distribution categories on ischaemic stroke are also shown in Table 4. The presence of CMBs (vs. no CMBs) was associated with a pooled risk ratio of recurrent ischaemic stroke of 1.8 (95% CI 1.4 to 2.5). Figure 8

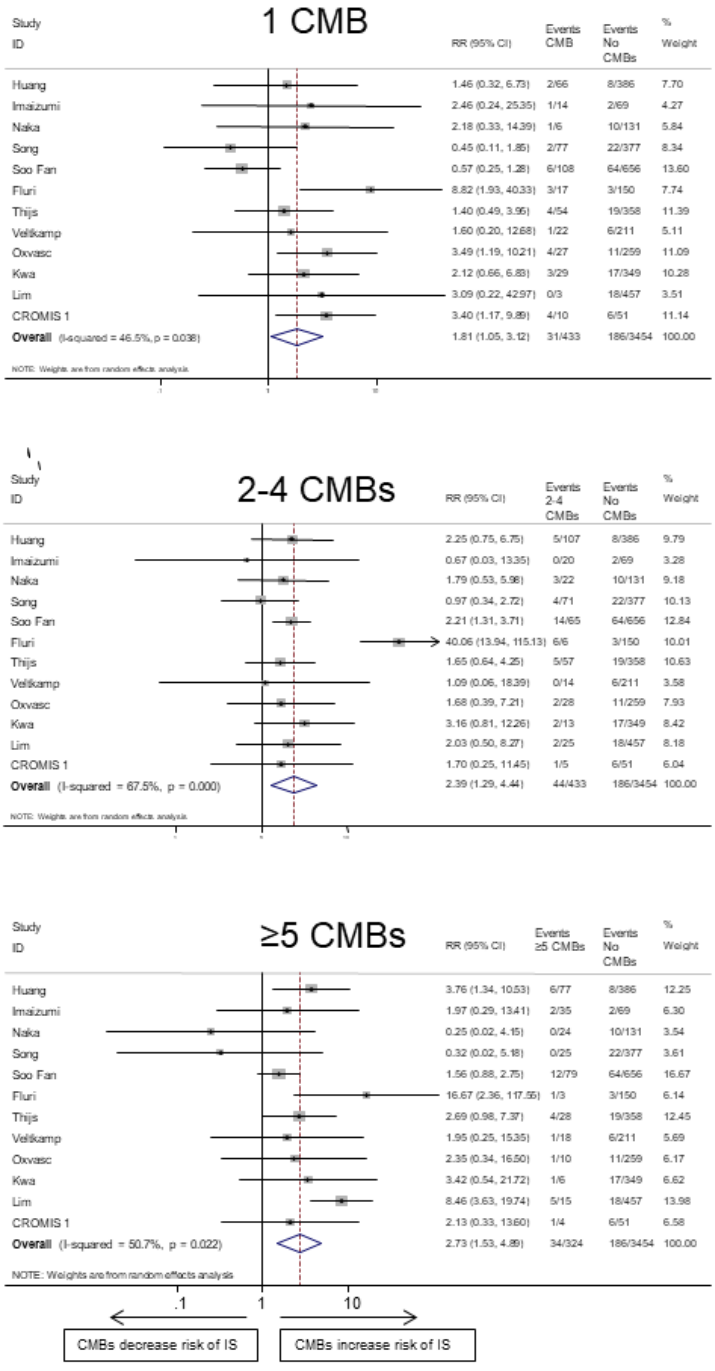
Figure 8 Pooled Risk Ratio of IS risk by CMB presence



Part 2: Ischaemic stroke populations

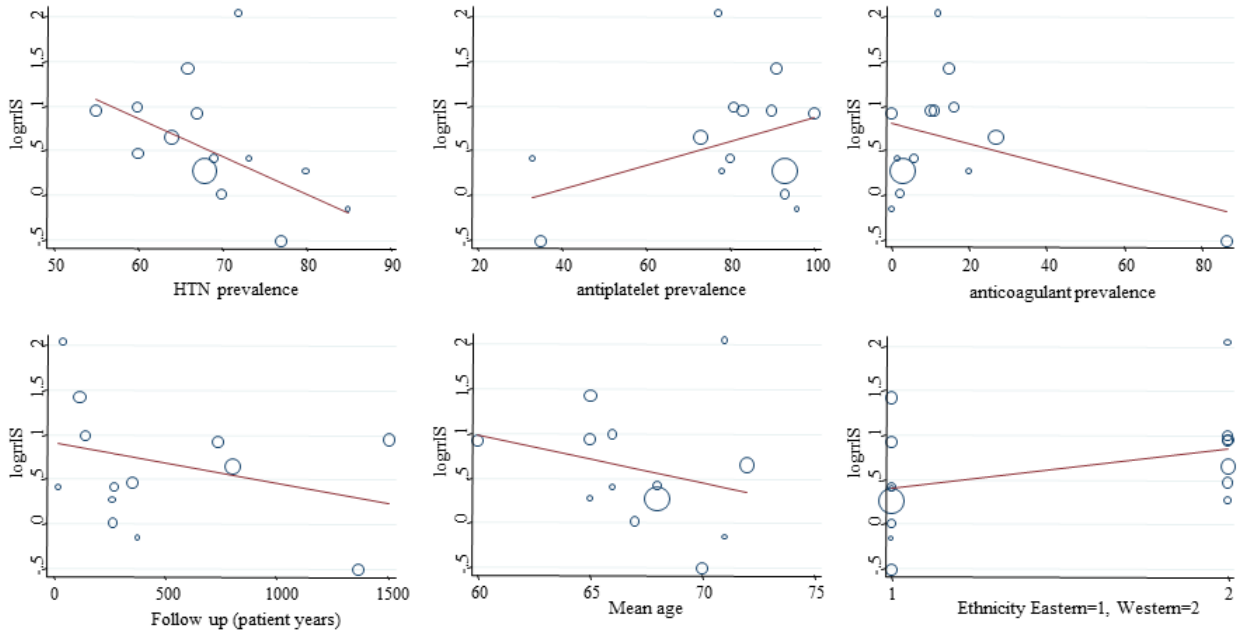
Funnel plots revealed no evidence of publication bias (Egger's test p=0.4). The presence of a single CMB (vs. no CMBs) had a pooled risk ratio for ischaemic stroke of 1.8 (95% CI 1.0 to 3.1). The pooled risk estimates for ischaemic stroke suggest an increasing trend toward higher ischaemic stroke risk with increasing CMB burden. (Table 4, figure 9).

Figure 9 Ischaemic stroke risk by CMB burden



Logistic regression was used to estimate the increase in risk for each additional CMB; this showed an odds ratio of 1.10 (95% CI 1.06 to 1.14) per CMB increase. The risk estimates for ischaemic stroke for each distribution category of CMBs (vs. no CMBs) ranged from 1.6 (95% CI 1.0 to 2.7) for strictly deep CMBs to 2.6 (95% CI 1.5 to 4.3) for mixed CMBs, with overlapping confidence intervals for all groups. Because we noted statistical heterogeneity among the cohorts for ischaemic stroke risk (I^2 33%, 47%, 68% and 51% respectively for CMB presence, 1 CMB, 2-4 CMB and ≥5 CMB respectively), each potential confounder (ethnicity, average follow up, age, hypertension prevalence and antithrombotic use) was investigated separately using meta regression. We found only weak evidence for a confounding effect of hypertension showing the effect CMBs have on ischaemic stroke risk is less in studies with a higher prevalence of hypertension. (Figure 10)

Figure 10 Meta-regression plots showing the relationship between intra-study variability and the effect of CMBs on the relative risk of future ischaemic stroke



CMBs and intracerebral haemorrhage (ICH) risk.

The total ICH rate was 66/5068 (1.3%). The ICH event rate in those with CMBs was 4.3% (49/1142) vs. 0.5% (17/2912) for those without CMBs; thus, CMBs confer an absolute risk increase of 3.8% for ICH. The absolute risk increase for ICH for CMBs vs. no CMBs increases as the CMB burden increases (1.7% for 1 CMB, 1.8% for 2-4 CMBs and 8.2% for ≥5 CMBs (table 4)).

The risk ratios for different CMB burden and distribution categories on ICH are also shown in Table 4. The presence of CMBs (vs. no CMBs) was associated with a pooled risk ratio of 6.3 for subsequent ICH (95% CI 3.5 to 11.4) Figure 11. Four studies were excluded, as they did not report any ICH outcomes. Increasing CMB burden was associated with an increased risk of ICH (pooled risk ratio 4.6 (95% CI 1.9-10.7), 5.6 (95% CI 2.4-13.3); and 14.1 (95% CI 6.9-29.0) for 1 CMB, 2-4 CMBs and ≥5 CMBs compared to no CMBs, respectively) (Table 4, figure 12). Logistic regression showed an odds ratio of 1.29 (95% CI 1.21 to 1.37) for ICH per additional CMB. Of the CMB anatomical distribution categories (strictly lobar, mixed, or strictly deep), strictly lobar CMBs were associated with the highest risk of subsequent ICH vs. no CMBs (pooled risk ratio 10.5 (95% CI 4.5-24.3); Table 4). There was no publication bias within studies (Egger's test p=0.98). Meta-regression was not undertaken because heterogeneity was not detected (I^2 was 0%) for ICH outcomes.

Figure 11 Risk of ICH by CMB presence

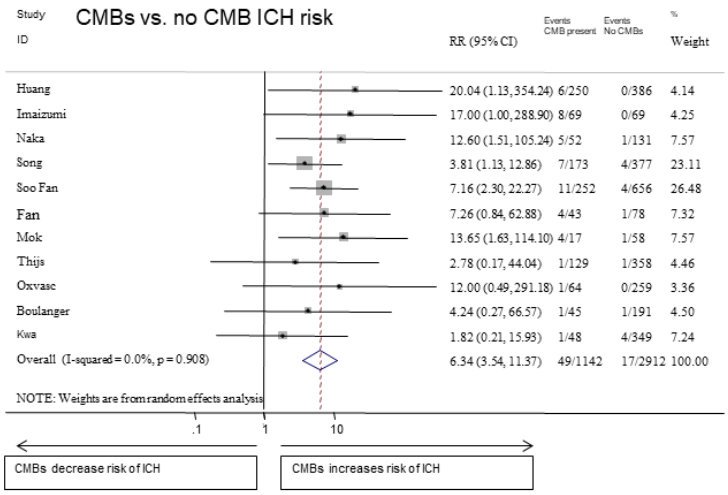
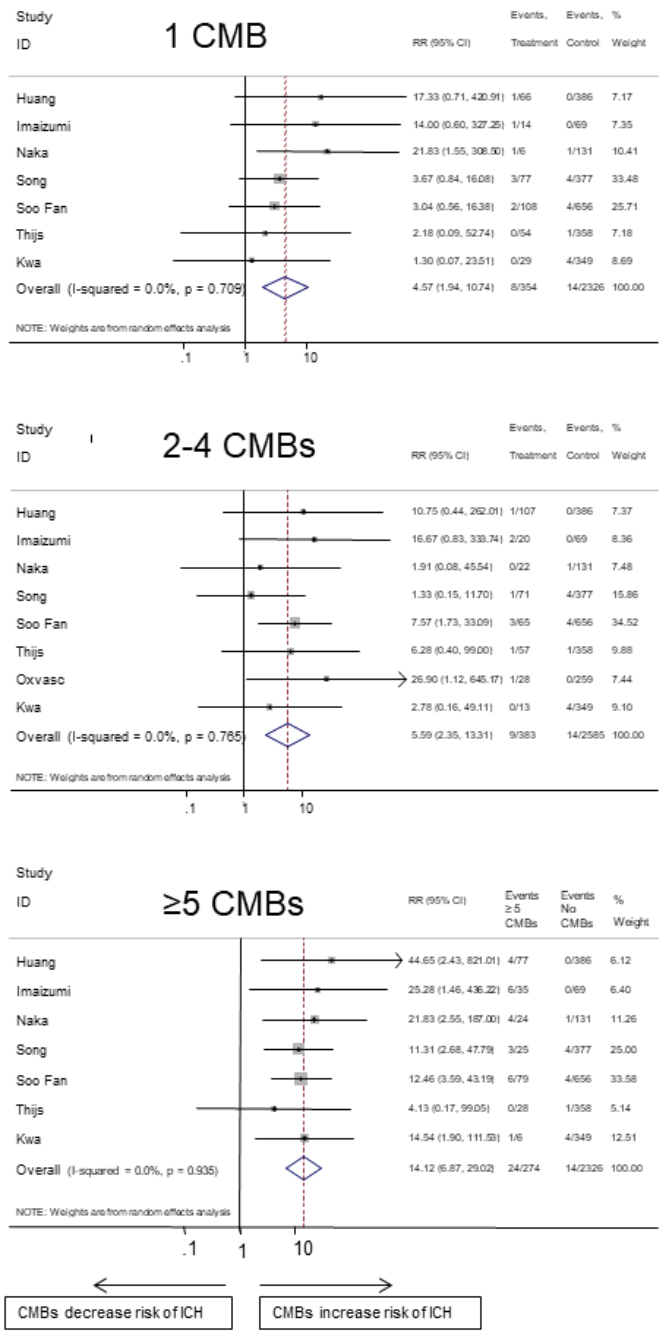


Figure 12 Intracerebral haemorrhage risk by CMB burden



5.4 Discussion

Our meta-analysis of 15 prospective studies, including more than 5000 patients presenting with ischaemic stroke or TIA, found that the presence of any CMBs is associated with an approximate doubling of the risk of ischaemic stroke, but with an approximately 6-fold increase in the risk of ICH, in keeping with two previous smaller meta-analyses (119, 200). Our meta-analysis also builds on these previous studies and adds new knowledge on ICH risk: first, we were able to increase our statistical power by including more ICH outcomes(119); second, by pooling aggregate data we investigated how increasing CMB burden affects the balance between future ischaemic stroke and ICH (including both relative and absolute risks); and third, we partially adjusted for confounding factors through meta-regression. Our most important new finding is that with increasing CMB burden the risk of ICH increases more steeply than that of ischaemic stroke. In patients with ≥5 CMBs the risk of ICH was substantially higher than that of ischaemic stroke (risk ratio for ICH 14.1 (95% CI 6.7-29.0) vs. risk ratio for ischaemic stroke 2.73 (95% CI 1.5-4.9)). In a complementary logistic regression analysis, we showed that each additional CMB is associated with increased odds of 1.3 (95% CI 1.2 to 1.4) for ICH and 1.1 (95% CI 1.1 to 1.1)) for ischaemic stroke, supporting a steeper increase in ICH than ischaemic stroke risk with higher CMB burden. However, the absolute event rate of recurrent ischaemic stroke was consistently higher than the absolute event rate of ICH in patients with CMBs and within all CMB categories, including those with ≥5 CMBs.

A large number of CMBs (e.g. ≥5 CMB) might help identify patients at substantially higher risk of ICH than of ischaemic stroke. Indeed, for clinicians, the key question is what burden of CMBs could tip the balance of risk towards ICH sufficiently to affect clinical decisions, for example antithrombotic drug use. Antiplatelet agents only modestly reduce the absolute risk of ischaemic stroke in secondary prevention (0.5 to 2.5%)(201). Our data show the absolute risk of ICH increases substantially more than the absolute risk of ischaemic stroke as CMB burden increases; the effect is most evident with ≥5 CMBs, which is associated with an 8.2% absolute risk increase for ICH vs a 5.1% absolute risk increase for ischaemic stroke). This raises the possibility that antiplatelet drug risk-benefit assessment may favour avoiding their use in those with numerous CMBs (e.g. ≥5 CMBs). This could affect a substantial proportion of ischaemic stroke and TIA patients; of patients with CMBs, the

prevalence of those with ≥5 CMBs ranged from 12 to 51% in studies included in this analysis and varied by ethnicity (mean 17% for Western cohorts and 35% for Eastern cohorts).

A previous meta-analysis suggested that ethnicity may be an important determinant of the balance of ICH and ischaemic stroke risks associated with CMBs; an increased risk for ICH risk was only statistically significant in Eastern cohorts, while ischaemic stroke risk was only significant in Western cohorts (119). In the present study we included more patients, and using meta-regression found that ethnicity does not confound the association between CMB burden and ischaemic stroke or ICH risks. Thus, based on the current study, CMB burden appears to be a greater predictor of ischaemic stroke and ICH risk than ethnicity.

Our study has several strengths, including a large sample size from multiple cohorts from different countries. We only included those of high quality using systematic quality indicator assessment. We included data on CMB burden and distribution, and adjusted for confounding factors through meta-regression. Our study thus provides best currently available evidence on how CMBs affect ischaemic stroke and ICH risk after ischaemic stroke or TIA.

Our study also has limitations. Because we included aggregate summary-level data (rather than individual patient data), we could not explore the effect of CMB distribution free from the confounding effect of CMB burden. The mixed CMB category has the highest risk of stroke, but by definition includes only patients with multiple CMBs; by contrast, the strictly lobar and strictly deep CMB categories could include patients with a single CMB. Specifically, we could not fully investigate the independent risk associated with strictly lobar CMBs, critical to the diagnosis of cerebral amyloid angiopathy (CAA) (91) with high recurrent ICH risk (126) (108). Although we undertook meta-regression, this can only partially account for confounding and is unlikely to fully account for variables such as age and hypertension. Our logistic regression assumes an average CMB count within each category (difficult to estimate in the open ended ≥10 CMB category) and that the log-odds of ICH/ischaemic stroke increase linearly with CMB burden. However, consistent findings

from two complementary statistical analyses strongly support the hypothesis that increasing CMB burden increases the risk of ICH more than that of ischaemic stroke. Further limitations include the variable study sample size and follow up, which may bias our results, especially regarding ICH, a rare outcome with wide confidence intervals around risk estimates (which overlap for the different CMB burden categories). A time to event analysis may have been a more appropriate statistical method given the varying follow up, but this was not possible with the data available. Imaging protocols and analysis were similar but not completely uniform; field strength (202) echo time (203) and optimised paramagnetic sequences (204) can all influence CMB detection. However, most studies were performed at 1.5T with echo times within a narrow range, making this unlikely to affect our conclusions. Nevertheless, our results are only generalizable to patients scanned on 1.5 tesla MRI using gradient recalled echo and may not be applicable to SWI or MRI with a higher field strength. SWI increases the number of CMB detected (204, 205) compared to T2*-weighted images; CMB burden categories may thus have to be revised for SWI. Finally, studies used different methods for CMB rating; standardised rating instruments (88, 206, 207) may improve the reliability of defining CMB categories, particularly that of a single CMB.

Although our study provides important new information, to fully determine how CMBs might influence antithrombotic decisions, the interaction between CMBs and antiplatelet agents and anticoagulants needs to be further addressed in large prospective studies. Although the prevalence of antithrombotic and anticoagulant use did not show an association with either ICH or ischaemic stroke outcome in our meta-regression, most patients we included were treated with antiplatelet agents. Very few patients included in our meta-analysis were on anticoagulation; more data are therefore needed on this group, who may be at highest ICH risk. Ongoing prospective observational studies addressing this question include www.ucl.ac.uk/cromis-2(208), and https://clinicaltrials.gov/ct2/show/NCT02238470. Further pooled analyses of individual patient data from these and other observational studies – and, ultimately randomized controlled trials based on CMB burden - are needed to fully assess the interaction between CMBs and antithrombotic drugs (both antiplatelet agents and anticoagulants) after

ischaemic stroke and TIA. Nevertheless, we have shown that with increasing CMB burden, the risk of ICH increases more steeply than that of ischaemic stroke in a cohort of ischaemic stroke and TIA patients largely treated with antiplatelet medication. A high CMB burden (e.g. ≥5 CMBs) may identify patients at similar or greater risk of ICH than ischaemic stroke, with implications for antithrombotic treatment and future randomized controlled trials.

5.0 Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack: multicentre observational cohort study

Background: We aimed to determine whether cerebral microbleeds (CMBs) - a potential neuroimaging biomarker of bleeding-prone cerebral small vessel diseases – can identify patients at high risk of symptomatic intracranial haemorrhage when anticoagulated after recent ischaemic stroke or transient ischaemic attack (TIA).

Methods: Our observational, multi-centre, prospective inception cohort study recruited adults from UK hospitals with non-valvular atrial fibrillation (AF) and recent acute ischaemic stroke or TIA, treated with warfarin or a direct oral anticoagulant, and followed them up for 24 months using GP and patient postal questionnaires, telephone interviews, hospital visits, and NHS digital data on hospital admissions or death. We investigated baseline predictors of symptomatic intracranial haemorrhage using multivariable Cox regression and developed risk prediction models that we validated using bootstrapping.

Findings: We recruited 1490 participants between August 2011 and July 2015 (mean age 76 years; 631 (42%) female), with follow-up data available from 1447/1490 (97%) over a mean period of 850 (SD 373) days (3,366 patient-years). CMBs were present in 311/1490 (21%) and there were 14 symptomatic ICHs. The symptomatic intracranial haemorrhage rate in patients with CMBs was 10 per 1000 patient-years (95% CI 4-20) compared to 3 per 1000 patient-years (95% CI 1-5) in those without CMBs (adjusted hazard ratio 3·67 (95% CI 1·27-10·60)). CMBs were not significantly associated with recurrent ischaemic stroke (adjusted hazard ratio 1·53 (95% CI 0·85-2·76)). Compared to the HAS-BLED (Hypertension, Abnormal liver function, Abnormal renal function, Stroke, Bleeding history, Labile INR, Elderly, Drugs, Alcohol) score alone (C-index 0·41 (95% CI 0·29-0·53)), models including CMBs and HAS-BLED score (C-index 0·66 (95% CI 0·53-0·80)) and CMBs, diabetes, anticoagulant type and HAS-BLED score (C-index 0·74 (95% CI 0·60-0·88)) predicted symptomatic intracranial

haemorrhage significantly better (C-index (diff): 0·25 (95% CI 0·07-0·43, p = 0·0065); and 0·33 (95% CI 0·14-0·51, p < 0·00059, respectively).

Interpretation: In patients anticoagulated after recent ischaemic stroke or TIA, CMB presence is independently associated with symptomatic intracranial haemorrhage risk, improves the predictive ability of clinical risk scores, and can inform anticoagulation decisions.

Funding: CROMIS-2 was funded by the Stroke Association and the British Heart Foundation.

5.1 Rationale for study

Atrial fibrillation (AF) increases the risk of ischaemic stroke five-fold (209). In most individuals, oral anticoagulation with either vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) is indicated because they reduce the risk of ischaemic stroke by about two-thirds, with only a minimal increase in extra-cranial haemorrhage.(210, 211) However, a devastating and unpredictable complication of oral anticoagulation is anticoagulant-related symptomatic intracranial haemorrhage, which has 42% in-hospital mortality, and causes substantial disability in survivors (212). There is an unmet important clinical need to reliably predict the risk of intracranial haemorrhage, and differentiate this from the risk of ischaemic stroke, to allow clinicians to assess the likely net clinical benefit of oral anticoagulation. Risk scores including clinical factors such as hypertension and age have been developed to help clinicians identify patients at high risk of bleeding on anticoagulation, for example HAS-BLED (213), HAEMORR$_2$HAGES (214) and ATRIA (215), but these are of limited value in clinical decision-making because they predict both ischaemic stroke and intracranial haemorrhage.

Cerebral microbleeds (CMBs) are small hypointense round or ovoid areas identified on blood-sensitive MRI sequences (T2*-weighted gradient-recalled echo (GRE) or susceptibility-weighted imaging (SWI))(11, 88). In most cases CMBs correspond pathologically to small clusters of haemosiderin-laden macrophages resulting from small self-limiting haemorrhages(89, 93). Thus, CMBs are a promising radiological biomarker of the bleeding-prone cerebral small vessel diseases that cause most spontaneous intracerebral haemorrhages(11), so might be a specific and clinically useful predictor of anticoagulant-related intracranial haemorrhage. The increasing use of blood-sensitive MRI has led to increased detection of CMBs in patients with ischaemic stroke - including those with AF, where they are seen in up to 30% of patients (216) - generating considerable clinical uncertainty about the risk-benefit balance of anticoagulation in patients with CMBs.

We did a large observational prospective multi-centre inception cohort study to determine if CMBs are independently associated with an increased risk of symptomatic intracranial haemorrhage in patients with recent acute ischaemic stroke or TIA with AF treated with anticoagulation. We also developed and internally validated a risk prediction score for symptomatic intracranial haemorrhage including CMB presence as a neuroimaging biomarker in addition to clinical risk factors.

5.2 Methods:

5.2.1 Study design and participants

CROMIS-2 (AF) is an observational multicentre prospective inception cohort study which recruited adults with non-valvular AF (verified by ECG), who presented with ischaemic stroke or TIA, and were identified by the treating physician for anticoagulation treatment. We did not strictly control the timing of oral anticoagulation, which depended on individual clinician best judgement according to standard practice in the UK. We excluded patients if they could not undergo MRI, had a definite contraindication to anticoagulation, or had previously been treated with anticoagulation. We collected screening logs from centres to assess selection bias. We collected detailed clinical and demographic baseline data, and follow-up information from patients and general practitioners at 6, 12 and 24 months via standardised structured postal questionnaires or telephone interviews. We obtained National Health Service Digital data regarding hospital admissions or death during follow-up. If an outcome event was reported, we obtained additional clinical and radiological details from treating clinical teams and medical records to allow central adjudication, blinded to baseline neuroimaging findings.

Our planned sample size (n=1425) was calculated to detect a relative risk of 4.0 for intracranial haemorrhage risk associated with CMBs, assuming an annual incidence of intracerebral haemorrhage of 1·25% in those without CMBs, and that 20% of our population would have CMBs; these values were derived from previous smaller studies(208).

5.2.2 Neuroimaging data.

All patients underwent baseline MRI brain imaging according to a pre-defined protocol parameter range designed to detect relevant markers of cerebrovascular disease (208) which required T2*-weighted GRE (echo time (TE) 10 to 45ms), axial T1, Axial T2, coronal FLAIR and diffusion-weighted imaging with apparent diffusion coefficient maps. MRIs were analysed for markers of cerebral small vessel disease defined according to consensus definitions(11) using validated scales where available. We used the Microbleed Anatomical Rating Scale to identify and classify CMBs as lobar or non-lobar (deep, including the basal ganglia, thalamus, deep white matter, brainstem and cerebellum); white matter hyperintensities were rated using the Fazekas and Age-

Related White Mater Changes (ARWMC) scales).(207, 217, 218) Cortical superficial siderosis (cSS) was defined using consensus criteria(132, 137, 144). All neuroimaging ratings were done by a clinical research fellow (DW) trained by a professor of neuroradiology with specialist interest in cerebrovascular disease (HRJ). A second trained clinical fellow (GB) rated a random 10% of the sample for CMB presence; we quantified intra- and inter-rater reliability for CMB presence using Cohen's kappa coefficient.

5.2.3 Outcome events:

Two professors of vascular neurology (DJW and MMB) and a clinical research fellow (DW) adjudicated all primary outcome events (symptomatic intracranial haemorrhage; defined as brain-imaging evidence of non-traumatic spontaneous intracranial haemorrhage with appropriate clinical symptoms). A trained clinical research fellow (DW) adjudicated all ischaemic stroke outcomes; to ensure consistency a random 10% of these were adjudicated by a professor of vascular neurology (DJW) and a professor of neuroradiology (HRJ). All adjudication was blinded to baseline CMB ratings. In cases of disagreement, we reached consensus after discussion. We also collected information on death, cardiac ischaemic events (defined by dynamic ECG changes and/or troponin rise), and any major bleeding during follow-up (defined as intracranial bleeding or extracranial bleeding in either a critical area or requiring hospitalisation and two units of blood transfusion(219)).

5.2.4 Statistical analysis.

We followed a pre-specified statistical analysis plan outlined in our published protocol(208). We compared baseline demographics and risk factor profiles between those with CMBs and those without CMBs, and between those with and without our primary outcome event (symptomatic intracranial haemorrhage). We used appropriate statistical measures for categorical and continuous measures. We visually inspected the distribution of continuous variables using histograms, summarised as means with standard deviation or medians with interquartile range (IQR). Groups were compared using the Mann-Whitney test if they were not normally distributed or the t-test if normally distributed; categorical variables were compared between groups with the chi-squared test or, where appropriate, Fisher’s exact test. Univariate Kaplan-Meier survival

probabilities were estimated for those with and without CMBs; we used the log-rank test to compare groups. We performed univariable and multivariable Cox regression (adjusted for age and history of hypertension, in keeping with our pre-specified statistical analysis plan). We did three further multivariable Cox regression sensitivity analyses: first, including variables strongly associated with intracranial haemorrhage in univariate analysis; second, including CMB presence and HAS-BLED – a commonly used clinical bleeding risk score(220); and third, including other neuroimaging markers of small vessel disease in addition to CMB presence. We assessed the proportional hazards assumption through visual inspection of log-log plots of the log cumulative hazard against log time. We calculated absolute event rates per 1000 patient-years for our primary outcome of symptomatic intracranial haemorrhage, and for our main secondary outcome of recurrent ischaemic stroke. For our secondary outcome of recurrent ischaemic stroke, we adjusted for variables which differed between those who did and did not have a recurrent ischaemic stroke at the 20% level.

Finally, we developed two prediction models using Cox regression: in the first we included all predictors significantly associated with intracranial haemorrhage at the 20% level in univariable analysis; in the second we included CMB presence and HAS-BLED score. We assessed calibration using the Cox calibration slopes, and quantified discrimination using Harrell's C-index. We used bootstrapping to validate the models; specifically, the models were re-fitted in 1000 bootstrap samples and applied to the original dataset. For each model, we then calculated the calibration slope and optimism-adjusted C-index (221). We also fitted these models using the lasso(222) to investigate possible over-fitting. We did all statistical analysis using STATA 12.0 (StataCorp LP, TX).

5.2.5 Ethical approval

CROMIS-2 was approved by the National Research Ethics Committee, London Queen Square. Patients with capacity gave informed written consent. When patients could not consent, we obtained written consent from a proxy as defined by relevant local legislation.

5.2.6 Funders

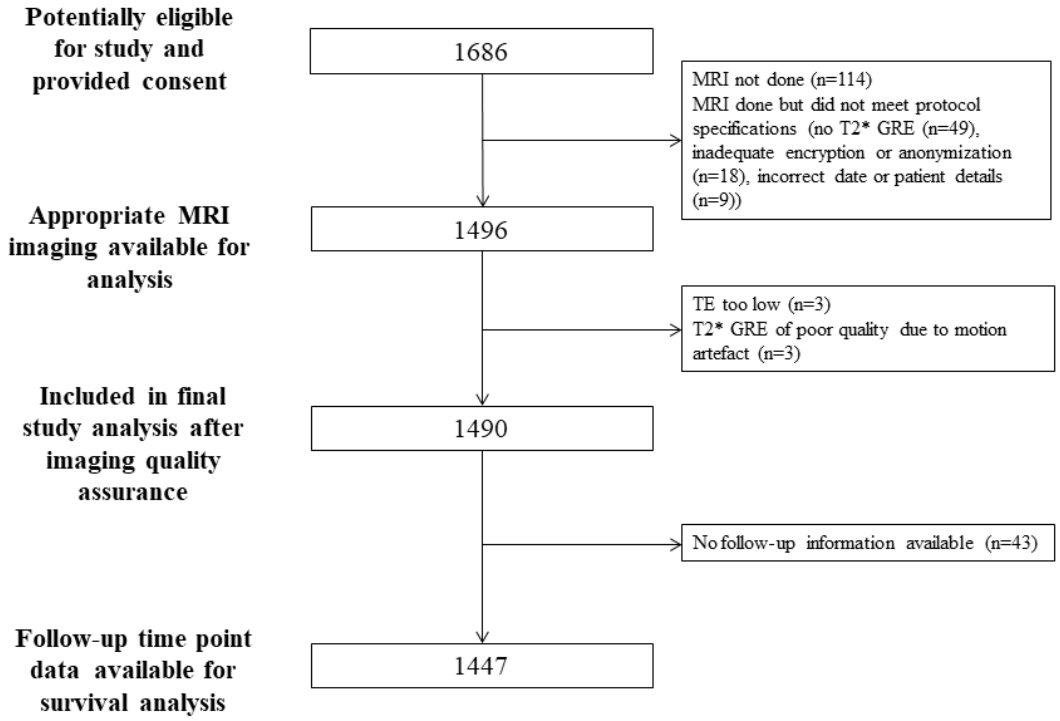
CROMIS-2 was jointly funded by the Stroke Association and the British Heart Foundation and supported by researchers at the National Institute for Health Research (NIHR) University College London Hospitals Biomedical Research Centre. UCL acted as the Sponsor for CROMIS-2, with responsibility for the conduct and management of the study. Neither the funders nor the sponsor had input into study design; collection, analysis, or the interpretation of data.

5.3 Results

5.3.1 Cohort characteristics

1686 patients were potentially eligible and initially consented from 79 centres across the UK (and one centre in the Netherlands) between August 2011 and July 2015. Patients were only included in the final analysis if they underwent MRI with T2*-weighted GRE sequences of adequate technical quality to rate CMBs. After imaging quality assurance, we included 1490 participants in our final analysis (1294/1490 (87%) with 1.5 Tesla scans and 196/1490 (13%) with 3 Tesla scans); patient flow through the study is shown in Figure 13.

Figure 13 Study entry flow diagram



Part 2: Ischaemic stroke populations

There were no significant differences in demographics, stroke risk factors or stroke severity (National Institutes of Health Stroke Score, NIHSS) between patients included (n=1490) compared to those consented but not included (n=196). We collected screening logs from 26 sites to assess selection bias; compared to those included, 614 patients who were eligible but not consented were older (mean 80 vs. 75 years, p<0·0001), more likely to be female (252/640 (55%) vs. 213/506 (42%), p<0·0001), and had more severe strokes (median baseline NIHSS 8 vs. 5, p<0·0001).

Of 1490 patients included, 1447 (97%) had follow-up information available. The mean age was 76 years (SD 10); 631 (42%) were female; other baseline characteristics are shown in Table 5. The 43 patients without follow-up did not differ to those followed up in age (76 vs. 73, p=0·1656), hypertension (23/40 (58%) vs. 907/1427 (64%), p=0·43) or CMB prevalence (7/43(16%) vs. 304/1447 (21%), p=0·45).

Table 5 Characteristics of patients with and without cerebral microbleeds at baseline

Variable		All patients n=1490	Patients with CMBs n=311	Patients without CMBs n=1179
Age, years mean (SD)		76 (10)	78 (10)	75 (10)
Sex, female, n (%)		631 (42)	129 (41)	502 (43)
Hypertension n (%)		930 (63)	212 (70)	718 (62)
Hyperlipidaemia n (%)		661 (45)	145 (47)	516 (44)
Diabetes mellitus n (%)		251 (17)	55 (18)	196 (17)
Ischaemic heart disease		243 (16)	66 (21)	177 (15)
Previous ischaemic stroke n (%)		142 (10)	41 (13)	101 (9)
Previous intracerebral haemorrhage n (%)		8 (0·54)	3 (1·0)	5 (0·4)
Alcohol use units/week median (IQR)		2 (0 to 9)	2 (0 to 7)	2 (0 to 10)
Alcohol use >14 units/week n (%)		213 (15)	43 (15)	170 (16)
Congestive heart failure n (%)		60 (4)	20 (6)	40 (3)
Abnormal renal function n (%)		174 (12)	46 (15)	128 (11)
Ethnicity	**White n (%)**	1414 (96)	290 (95)	1124 (97)
	Asian n (%)	33 (2)	10 (3)	23 (2)
	Black n (%)	20 (1)	5 (2)	15 (1)
CRP median (IQR)		4.6 (2 to 12)	4.4 (2 to 12)	4.9 (2 to 11)
Platelet count median (IQR)		221 (185 to 265)	221 (185 to 265)	222 (183 to 265)
HAS-BLED score median (IQR)		3 (2 to 3)	3 (2 to 4)	3 (3 to 4)
CHA_2DS_2VASc score median (IQR)		5 (4 to 6)	5 (4 to 6)	5 (4 to 6)
Anticoagulation started n (%)		1436 (96)	300 (96)	1136 (96)
DOAC use n (%) (in the 1436 patients who started anticoagulation)		542 (37)	121 (40)	421 (36)
Concurrent antiplatelets n (%)		57 (4)	48 (4)	9 (3)
Poor time in therapeutic range n (%)		133/894 (15)	24/179 (13)	109/715 (15)
Anticoagulation stopped during follow-up (in the 1436 patients who started anticoagulation)		55 (4)	13 (4)	42 (4)
Total white matter hyperintensity (ARWMC) score median (IQR)		1 (0 to 3)	2 (1 to 4)	1 (0 to 3)
CMB median (IQR) **CMB range**			1 (1 to 3) 1 to 107	N/A
cSS presence n (%)		5 (0·34)	1 (0·32)	4 (0·34)

CMBs were present in 311 (21%) of 1490 participants; in those with CMBs the median CMB count was 1 (IQR 1 to 3; range 1 to 107). Intra-rater and inter-rater reliability for the presence of CMBs were excellent (Kappa 0·93 (95% CI 0.86 to 1.00) and 0.85 (95% CI 0.74 to 0.96) respectively). CMBs were strictly lobar in 116 patients; strictly non-lobar (deep) in 120 patients; and mixed in 75 patients. 46 patients (3%) fulfilled the modified Boston criteria for cerebral amyloid angiopathy(137). Five patients (0.34%) had cSS (in one patient this was disseminated). 432/1490 (29%) had severe white matter hyperintensities (ARWMC score(217) ≥2 in either basal ganglia or white matter regions). The characteristics of patients with and without CMBs are shown in Table 5.

5.3.2 Primary outcome

The 1,447 patients with follow-up available provided 3,366 patient-years of follow-up data (mean follow-up 850 days (SD 373 days)). There were 14 symptomatic intracranial haemorrhages: 11 intracerebral haemorrhages; two subdural haemorrhages; and one subarachnoid haemorrhage. Patients who had a symptomatic intracranial haemorrhage during follow-up had a higher prevalence of diabetes (6/14 (43%) vs. 245/1474 (17%)), were more likely to be on a VKA than DOAC (12/14) (86%) vs. 882/1422 (63%)) and more likely to have CMBs (7/14 (50%) vs. 304/1476 (21%)) and cortical superficial siderosis (1/14 (7%) vs. 4/1476 (0·3%)) compared to those who remained free of intracranial haemorrhage (Table 6).

Table 6 Characteristics of patients with and without symptomatic intracranial haemorrhage

Variable		Patients with symptomatic intracranial haemorrhage (n=14)	Patients without symptomatic intracranial haemorrhage (n=1433)	p value
Age, years median (IQR)		79 (10)	76 (10)	0·32
Sex, female, n (%)		5 (36)	606 (42)	0·62
Hypertension n (%)		8 (57)	898 (64)	0·62
Hyperlipidaemia n (%)		8 (57)	653 (45)	0·36
Diabetes mellitus n (%)		6 (43)	236 (17)	0·0086
Ischaemic heart disease		1 (7)	238 (17)	0·34
Previous ischaemic stroke n (%)		2 (15)	138 (10)	0·50
Previous intracerebral haemorrhage n (%)		0 (0)	8 (0·6)	1·00
Alcohol units/ week median (IQR)		1.5 (0 to 5)	2 (0 to 9)	0·51
Alcohol use >14 units/week n (%)		1 (8)	212 (15)	0·50
Congestive heart failure n (%)		0 (0)	59 (4)	0.44
Abnormal renal function n (%)		169 (12)	2 (14)	0.77
Ethnicity	**White n (%)**	14 (100)	1356 (97)	
	Asian n (%)	0 (0)	29 (2)	
	Black n (%)	0 (0)	17 (1)	
Ethnicity non-white		0 (0)	46 (3)	0.49
CRP median (IQR)		5.5 (4.6 to 16.2)	4.4 (2 to 12)	0.11
Platelet count median (IQR)		212 (167 to 225)	220 (185 to 264)	0.25
CHA_2DS_2VASc score median (IQR)		6 (4 to 6)	5 (4 to 6)	0·23
HAS-BLED score median (IQR)		2 (2 to 3)	3 (2 to 3)	0·14
Anticoagulation started n (%)		14 (100)	1385(97)	0.49
DOAC use n (%)		2 (14)	510 (37)	0·081
Concurrent antiplatelets n (%)		1 (7)	56 (4)	0.54
Poor therapeutic time in range n (%)		0 (0)	133/862 (15)	0.145
Total white matter hyperintensity (ARWMC) score median (IQR)		1·5 (0 to 5)	1 (0 to 3)	0·97
CMB presence n (%) **CMB median (IQR)** **CMB range**		7 (50) 0.5 (0 to 3) 0 to 12	297 (21) 0 (0 to 0) 0 to 107	0·0075 0·0036 N/A
cSS presence n (%)		1 (7)	4 (0·3)	<0·0001

Key: Poor time in therapeutic range defined as <60%; ARWMC – age related white matter changes

In patients with a documented INR at the time of the intracranial haemorrhage (n=7), the median INR was 1·9 (IQR 1·4 to 4·0, minimum 1·1, maximum 4·8).

The symptomatic intracranial haemorrhage event rate in patients with CMBs was 10 per 1000 patient-years (95% CI 4 to 20) compared with 3 per 1000 patient-years (95% CI 1 to 5) in those without CMBs. The absolute rate increase associated with CMBs was 7 (95% CI 3 to 15) per 1000 patient-years (Table 7).

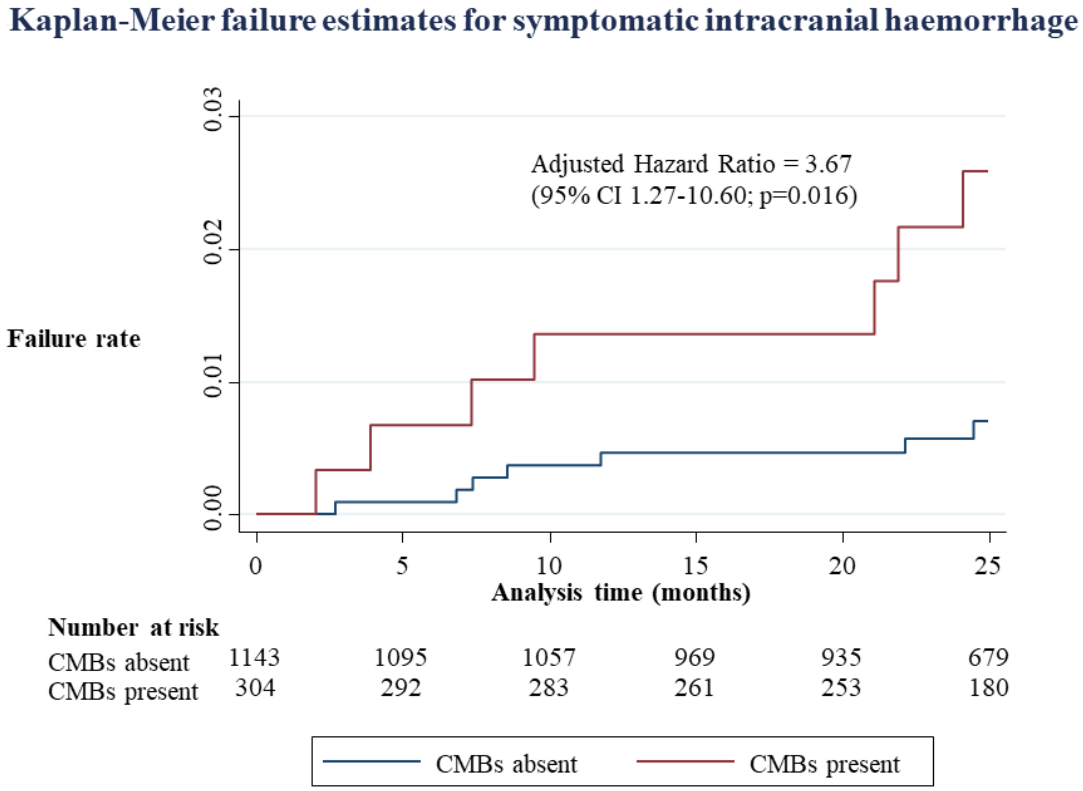
Table 7 Absolute event rates, absolute risks, univariable and multivariable HR for symptomatic intracranial haemorrhage and recurrent ischaemic stroke during follow-up, according to baseline CMB presence and burden.

	Symptomatic intracranial haemorrhage					Recurrent ischaemic stroke				
	Absolute event rate (n/patient-years)	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/1000 patient years (95% CI)**	**Univariable hazard ratio (95% CI)**	**Adjusted Hazard ratio (95% CI)***	**Absolute event rate (n/patient years)**	**Rate/1000 patient years (95% CI)**	**Absolute rate increase/1000 patient years (95% CI)**	**Univariable hazard ratio (95% CI)**	**Adjusted Hazard ratio (95% CI)****
No CMBs	7/2654	2·6 (1·1 to 5·4)	*Reference*	*Reference*	*Reference*	39/2608	15 (10·6 to 20·4)	*Reference*	*Reference*	*Reference*
CMB presence	7/712	9·8 (4·0 to 20·3)	7.2 (2.9 to 14.9)	3·73 (1·31 to 10·64)	3·67 (1·27 to 10·60)	17/704	24·1 (14·1 to 38·7)	9.1 (3.5 to 18.3)	1·62 (0·92 to 2·87)	1·53 (0·85 to 2·76)
1 CMB	2/367	5·4 (0·7 to 19·7)	2.8 (-0.4 to 14.3)	2·04 (0·42 to 9·84)	2·03 (0·42 to 9.83)	9/362	24·9 (11·4 to 47·2)	9.9 (0.8 to 32.2)	1·68 (0·82 to 3·47)	1·75 (0·84 to 3·65)
≥ 2 CMBs	5/345	14·4 (4·7 to 33·8)	11.8 (3.6 to 28.4)	5·58 (1·77 to 17·58)	5·46 (1·70 to 17·51)	8/341	23·4 (10·1 to 46·2)	8.4 (-0.5to 25.8)	1·56 (0·73 to 3·35)	1·32 (0·60 to 2·93)

* adjusted for age and hypertension
** adjusted for age, sex hypertension, diabetes, previous ischaemic stroke and white matter hyperintensities

Using the log-rank test for equality of survivor functions, symptomatic intracranial haemorrhages were more frequent in patients with CMBs compared to those without (p=0·0081). Univariable Cox regression showed that the hazard of symptomatic intracranial haemorrhage for patients with CMBs was 3·73 (95% CI 1·31 to 10·64) times higher than that for patients without CMBs. In multivariable Cox regression analysis adjusted for our pre-specified covariates (hypertension and age), the risk of symptomatic intracranial haemorrhage was 3·67 (95% CI 1·27 to 10·60) times higher for those with CMBs compared to those without CMBs (Figure 14, Table 7).

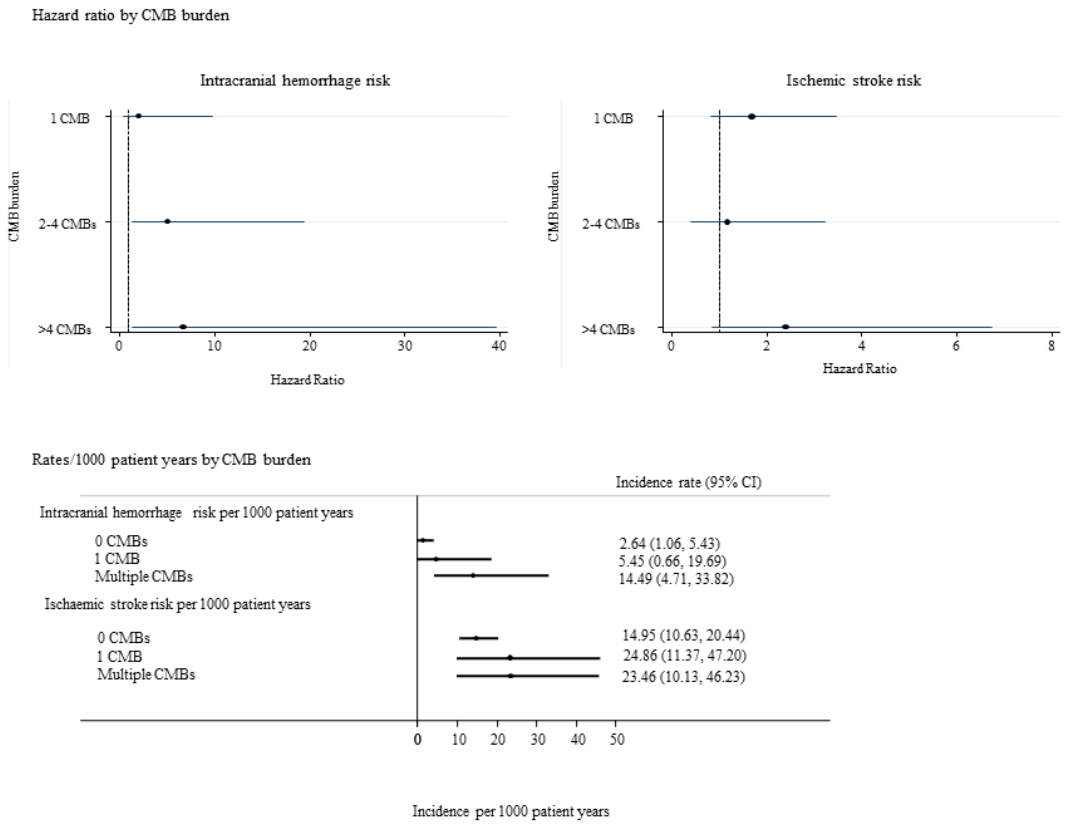
Figure 14 Kaplan-Meier analysis showing the probability of symptomatic intracranial haemorrhage (ICH) according to the presence or absence of microbleeds



Legend: CMB -cerebral microbleed, intracranial haemorrhage –symptomatic intracranial haemorrhage. Hazard ratio (HR), 95% confidence intervals (CI) are derived from model adjusted for hypertension and age

The risk of symptomatic intracranial haemorrhage increased with increasing CMB burden categories (defined as 0, 1 and ≥2 CMBs (p=0·00134)) (Table 7 and Figure 15).

Figure 15 Forest plots showing the incidence and hazard ratio with 95% confidence intervals of symptomatic intracranial haemorrhage and recurrent ischaemic stroke according to CMB burden



We also explored CMB distribution and rates of symptomatic intracranial haemorrhage, but there were too few events within each category to draw reliable conclusions (Table 8).

Table 8 Absolute event rates, risk increase and hazard ratios for symptomatic intracranial haemorrhage and ischaemic stroke according to CMB distribution

	Symptomatic intracranial haemorrhage			Recurrent ischaemic stroke		
	Absolute event rate (n/patient-years)	**Rate/1000 patient years (95% CI)**	**Hazard ratio (95% CI)**	**Absolute event rate (n/patient years)**	**Rate/1000 patient years (95% CI)**	**Hazard ratio (95% CI)**
No CMBs	7/2654	3 (1 to 5)	*Reference*	39/2608	15 (11 to 20)	*Reference*
Strictly lobar CMBs	3/243	12 (3 to 36)	3·31 (0·92 to 11·90)	4/243	16 (4 to 42)	0·94 (0·34 to 2·61)
Strictly Deep CMBs	1/285	0·3 (0·00 to 20)	0·83 (0·11 to 6·36)	8/278	29 (12 to 57)	1·82 (0·86 to 3·84)
Mixed CMBs	3/184	16 (3 to 48)	5·33 (1·23 to 23·07)	5/183	27 (9 to 64)	1·57 (0·55 to 4·50)
Multiple strictly lobar CMBs	1/91	11 (0·3 to 61)	2·45 (0·31 to 19.03)	2/89	22 (2 to 81)	1·20 (0·29 to 4·98)

We undertook three sensitivity analyses to confirm the robustness of the independent association of CMB presence with symptomatic intracranial haemorrhage, adjusting for other variables associated with this outcome; given the limited number of symptomatic intracranial haemorrhage events (n=14), we included a maximum of two variables in each multivariable analysis. CMB presence remained an independent predictor of intracranial haemorrhage as follows: first, adjusted for the two strongest univariable predictors (diabetes and anticoagulant type, but not cSS because of very few patients with cSS); HR 3·63; 95% CI 1·27 to 10·38 (Table 9); second, adjusted for HAS-BLED score (HR 5·64; 95% CI 1·79 to 17·80); and third, adjusted for other neuroimaging markers of small vessel disease (white matter hyperintensity score and cSS; HR 3·73 to 4·12, Table 10). For each model, visual inspection of the log-log plots suggested that the proportional hazards assumption was satisfactory.

Table 9 Cox regression analysis of the primary outcome (symptomatic intracranial haemorrhage) including CMBs and the two other strongest predictors from univariable analysis

Variable	HR	95% CI	p value
CMB presence	3·63	1·27 to 10·38	0·0160
DM	3·49	1·21 to 10·10	0·0210
DOAC use	0·31	0·07 to 1·38	0·1233

Table 10 Association of brain imaging markers of cerebral small vessel disease with symptomatic intracranial haemorrhage in univariable analyses, and effects of adjusting for each imaging marker on the association of CMB presence and symptomatic ICH

Variable	Definition of variable	Univariable Hazard Ratio for symptomatic intracranial haemorrhage (95% CI)	Hazard Ratio for CMB presence and symptomatic intracranial haemorrhage when each biomarker is entered as an 'adjustment variable'
White matter hyperintensities	Total ARWMC score	1·07 (0·86 to 1·34)	3·69 (1·26 to 10·74)
	Posterior predominant ARWMC	0·88 (0·20 to 3·94)	3·78 (1·32 to 10·79)
	Fazekas score dichotimised*	1·03 (0·32 to 3·29)	3·84 (1·33 to 11·10)
cSS	Any	24·78 (3·24 to 189·68)	4·12 (1·42 to 11·97)
	Disseminated**	N/A	3·73 (1·31 to 10·63)

Univariable hazard ratio for CMB presence alone: 3.73 (95% CI 1.31 to 10.64)
* Defined as a ARWMS score of 2 or above in either basal ganglia or deep white matter regions
** Defined as siderosis affecting 3 or more non-contiguous sulci

Of the 1490 patients recruited and identified by their treating physician to start anticoagulation, 1436 (96%) did so; 54 patients did not start because: 12 had died; 13 refused or did not attend their anticoagulation clinic appointments; 17 had medical contraindications; and for 12 the reason was not specified. The median time from stroke symptoms until starting anticoagulation was 11 days (IQR 4 to 17); 894/1490 (60%) patients started a VKA and 542/1490 (36%) patients started a NOAC. Repeat analyses including only anticoagulated participants (n=1436) did not significantly alter the results (univariable HR for CMB presence 3·73; 95% CI 1·31 to 10·63). The type of anticoagulant (DOAC or VKA) did not significantly affect the hazard of symptomatic intracranial haemorrhage associated with CMB presence (HR interaction term 0·88; 95% CI 0·04 to 17·13 p=0·92).

5.3.3 Secondary outcomes

Ischaemic stroke

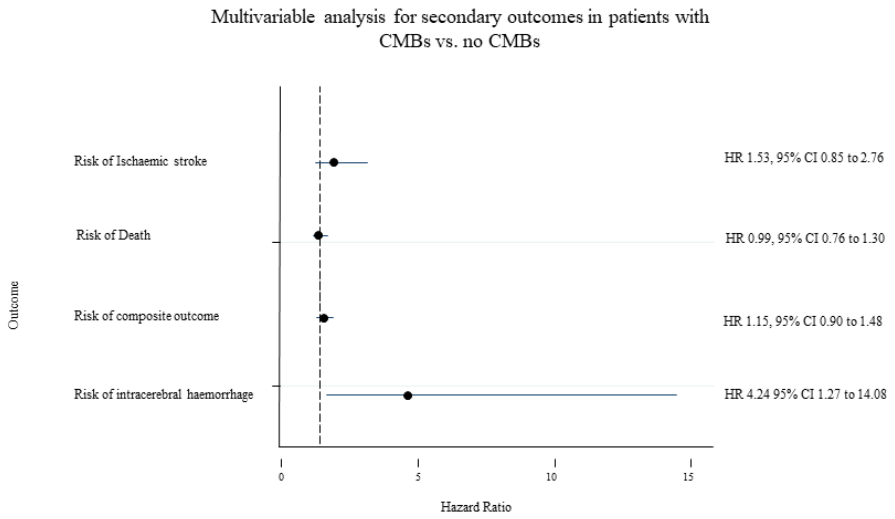
There were 56 recurrent ischaemic strokes during 3312 patient-years of follow-up. The recurrent ischaemic stroke rate in patients with CMBs was 24 (95% CI 14 to 39) per 1000 patient-years, compared to 15 (95% CI 11 to 20) per 1000 patient-years in those without CMBs; an increased ischaemic stroke rate associated with CMBs of 9 (95% CI 3 to 19) per 1000 patient-years. (Table 7). CMB presence was not significantly associated with recurrent ischaemic stroke in univariable (HR 1·62 95% CI 0·92 to 2·87) or multivariable analyses (adjusted for age, sex, hypertension, diabetes, previous ischaemic stroke prior to study entry, and WMH; (HR 1·53; 95% CI 0·85 to 2·76) (Table 7)).

The mortality following symptomatic intracranial haemorrhage during follow-up was significantly higher than that of recurrent ischaemic stroke (7/14 (50%; 95% CI 23 to 77%) vs 12/56 (21%; 95% CI 12 to 34%), p=0·041.

Intracerebral haemorrhage, death, composite outcome (death, ischaemic stroke, and symptomatic intracranial haemorrhage)

In multivariable analysis (adjusting for age and hypertension) CMB presence was associated with symptomatic intracerebral haemorrhage (HR 4·24; 95% CI 1·27 to 14·08) but not death or our composite outcome; Figure 16.

Figure 16 : Forest plots of the hazard ratio for secondary outcomes in participants with CMBs vs. those without CMBs



5.3.4 Prediction models

In Model 1 we included variables that were statistically significant at the 20% level in univariable analyses: CMB presence, Diabetes, NOAC use and HAS-BLED score; we excluded cSS due to its rarity, and time in therapeutic range for VKA because it is captured within HAS-BLED. Missing alcohol score values for HAS-BLED score were imputed using multiple imputation with chained equations(223) (10 imputations). Fitting a model with all four predictors (CMB presence, Diabetes, NOAC use and HAS-BLED score) produced an optimism-adjusted C-index of 0·74 (0·60 to 0·88).

In Model 2 we included CMB presence and HAS-BLED score (imputed for missing values as above), which produced an optimism adjusted C-index of 0·66 (95% CI 0·53 to 0·80).

Compared to the score HAS-BLED alone (C-index 0·41; 95% CI 0·29 to 0·53), Model 1 (C-index (diff): 0·33 (0·14 to 0·51), $p < 0·00059$) and Model 2 (C-index (diff): 0·25 (0·07 to 0·43), $p = 0·0065$) were both statistically better in predicting symptomatic intracranial haemorrhage.

5.4 Discussion

Our large prospective observational multi-centre cohort of patients with recent ischaemic stroke or TIA associated with AF clearly shows that baseline CMB presence is independently associated with an increased risk of symptomatic intracranial haemorrhage. We note, however, that the absolute rate of recurrent ischaemic stroke was much higher than the absolute event rate of intracranial haemorrhage, even in those with CMBs. We also show that the addition of an imaging biomarker (CMB presence) improves the predictive ability of a clinical bleeding risk scores, which can help clinicians identify patients at high risk of intracranial haemorrhage.

Our results regarding CMB presence and intracranial haemorrhage risk are consistent with a previous smaller cohort study in a Korean hospital-based cohort study (n=550) of patients with ischaemic stroke and AF (122), which reported a similar increased in the risk of intracerebral haemorrhage associated with CMBs (HR 3·8; 95% CI 1·1 to 13·1) and a recent aggregate level meta-analysis(216). We found the use of DOAC rather than VKA was associated with a much lower incidence of intracerebral haemorrhage in participants with or without CMBs, consistent with the results of large randomised controlled trials(21). Our data therefore support previous speculation that DOACs might be considered in preference to VKAs in ischaemic stroke patients with AF and CMBs (224, 225). Our finding that diabetes is an independent risk factor for symptomatic intracranial haemorrhage has not, to the best of our knowledge, been previously reported in observational studies in ischaemic stroke patients. However, there is increasing evidence in non-stroke populations that diabetes is a risk for intracerebral haemorrhage: one large community-based study from China shows patients with diabetes had just over 1·5 times the risk of intracerebral haemorrhage than subjects with normal fasting blood sugars(226); another study in older patients with AF found patients with diabetes had 4·4 times the odds of major bleeding (mostly intracranial haemorrhages) than those who did not (227).

Our finding that CMBs were not significantly associated with ischaemic stroke differs from our recent meta-analysis of patients with recent ischaemic stroke or TIA(228), although this meta-analysis included a different population (mostly without AF and treated with antiplatelet therapy). The association of CMBs with future symptomatic intracranial haemorrhage but not ischaemic stroke risk in our cohort supports the hypothesis that CMBs are a biomarker of a bleeding-prone arteriopathy relevant for intracranial haemorrhage associated with anticoagulation. However, the relationship

between CMB presence and recurrent ischaemic stroke risk, while not statistically significant, was also in favour of a positive association. Thus, CMBs, as a marker of overall 'vascular fragility' might not be able to discriminate between intracranial bleeding and ischaemic stroke risks, but this important question requires further study. Indeed, the absolute event rate of ischaemic stroke in patients with CMBs (24.1 per 1000 patient-years) was much higher than the absolute event rate of symptomatic intracranial haemorrhage, even in patients with CMBs (9.8 per 1000 patient-years). By contrast to CMBs, white matter hyperintensities were not associated with symptomatic intracranial haemorrhage in our study, in keeping with data from two previous smaller similar cohorts(122, 123). This suggests that although both CMBs and WMH are markers of small vessel disease, only CMBs are related to future symptomatic intracranial haemorrhage bleeding risk. This observation also needs to be confirmed in larger cohorts.

A recent meta-analysis explored the risk of intracerebral haemorrhage in patients with five or more microbleeds(216), but we chose not to present hazard ratios for this subgroup because of the very low number of participants and event rates, which could lead to statistically unreliable results and over-interpretation. Whilst the event rates of symptomatic intracranial haemorrhage increased as CMB burden increased (and the event rate of recurrent ischaemic stroke remain stable), the limited number of participants with high CMB counts and limited number of primary outcome events did not allow us to establish whether there is a CMB burden threshold at which the absolute event rates of intracranial haemorrhage outweigh the event rates of ischaemic stroke (or, in other words, a CMB threshold at which anticoagulation might be clearly associated with net harm as judged by absolute event rates). We found that having only a single CMB was not statistically associated with a higher hazard of symptomatic intracranial haemorrhage, which might be because one CMB reflects only minor SVD, or because of limited inter and intra-rater reliability for one CMB(207, 229).

Our findings suggest that the addition of CMBs as a biomarker ('biological marker') to a clinical risk score might improve specificity and sensitivity in identifying ischaemic stroke and TIA patients at high risk of intracranial haemorrhage. Compared to using the clinical factor-based HASBLED score, the addition of CMBs to clinical risk models should better identify patients at high risk of intracranial haemorrhage to allow counselling, closer follow-up, rational anticoagulant choice, consideration of non-anticoagulant treatment options (e.g. left atrial appendage occlusion), and more

aggressive management of modifiable risk factors for intracranial haemorrhage (e.g. hypertension, anticoagulant monitoring and compliance). Large-scale collaborations are clearly required to develop more robust risk prediction scores. Nevertheless, based on our findings, we suggest that future risk scores to identify stroke patients at risk of intracranial haemorrhage should include neuroimaging biomarkers (CMBs and cortical superficial siderosis) in addition to clinical parameters.

Strengths and limitations

Our study has important strengths. We prospectively studied a large prospective inception cohort of patients at multiple hospital stroke units using standardised MRI sequences, which were rated for neuroimaging markers of small vessel disease using validated scales by a single trained observer. Our follow-up rate was 97%, and experienced observers adjudicated all primary events blinded to baseline CMB presence. We undertook survival analysis to consider baseline confounding factors and varying lengths of follow up, and we followed a pre-specified statistical analysis plan.

We also acknowledge limitations. Our cohort is likely to be affected by selection bias, as screening logs show that patients with more severe strokes were less likely to be enrolled. Nevertheless, our cohort is likely to be representative of patients with less severe strokes who are most likely to be considered for anticoagulation soon after their stroke. Our study had a low rate of symptomatic intracranial haemorrhage, limiting our ability to adjust for multiple confounders and the robustness of our risk prediction score. Although we standardised parameters for MR neuroimaging, the pragmatic clinical nature of our study meant different scanners were used, including different magnet strengths, which can influence CMB detection(202). Furthermore, gradient echo MRI sequences are less sensitive to CMBs than SWI(204), so that our interpretation of CMB-related risk may not translate to data from SWI. Treatment decisions might be influenced by clinical nihilism about intracranial haemorrhage compared to ischaemic stroke, so differences in judgement of the apparent severity of incident intracranial haemorrhage compared to ischaemic stroke may in part be artefacts of clinical behaviour.

In conclusion, we show that CMB presence is independently associated with an increased hazard of symptomatic intracranial haemorrhage. Nevertheless, the absolute incidence of symptomatic intracranial haemorrhage in our population of ischaemic stroke patients was three-fold lower than the incidence of recurrent ischaemic stroke.

The low incidence of symptomatic intracranial haemorrhage makes randomised control trials in this field unrealistic. Large-scale international pooled collaborative analyses will be essential to determine whether high CMB counts might be associated with an increased risk of intracranial haemorrhage sufficient to identify patients at net harm from oral anticoagulation.

PART 3

INTRACEREBRAL HAEMORRHAGE POPULATIONS

6.0 Developing an algorithm to identify patients with Intracerebral haemorrhage secondary to a macrovascular cause in young patients

Abstract

Introduction: Determining the cause of spontaneous (non-traumatic) intracerebral haemorrhage (ICH) is critical to guide treatment and prognosis. We investigated whether small vessel disease (SVD) in addition to clinical and other radiological findings on acute neuroimaging predicts a low risk of a macrovascular cause (e.g. an arterio-venous malformation, aneurysm, or dural arteriovenous fistula).

Patients and Methods: We identified patients with acute spontaneous ICH who underwent acute non-contrast CT, CT angiography (CTA) and intra-arterial digital subtraction angiography (IADSA) at our institution from January 2010-April 2014. Logistic regression including CTA result, SVD, age, pre-ICH hypertension and ICH location was used to derive a prediction model, validated using bootstrapping.

Results: 173 patients (46% female, median age 49) of whom 78 had a macrovascular cause on IADSA were included. Predictors of a macrovascular cause were: abnormal CTA (OR 67.4; $p<0.001$); absence of SVD (OR 5.0; $p=0.019$); and absence of pre-ICH hypertension (OR 3.4; $p=0.05$). In our internally-derived prediction model, the combination of CTA, SVD and pre-ICH hypertension predicted the likelihood of an underlying macrovascular cause (optimism-adjusted ROC area 0.919). Patients with negative CTA, SVD and pre-ICH hypertension have a low likelihood of an underlying macrovascular cause (1.8%).

Discussion and Conclusion: A combination of CTA, SVD and pre-ICH hypertension predict the likelihood of finding a macrovascular cause in patients with acute spontaneous ICH, allowing informed decisions regarding the likely benefit and risk of IADSA.

6.1 Rationale for study

Intracerebral haemorrhage (ICH) is devastating: mortality is 54% at 1 year (3), while only 12-39% of survivors recover to independence (4). Most cases (77–88%) of spontaneous (non-traumatic) intracerebral haemorrhage are termed "primary" (230), with a presumption that they are caused by small vessel disease (SVD) (33). However, it is critical to exclude "secondary" structural causes of ICH, including macrovascular causes (e.g. arterio-venous malformations, aneurysms, and dural arteriovenous fistulae), which can be treated.

The "reference standard" for detection of a macrovascular cause is intra-arterial digital subtraction angiography (IADSA) or neurosurgery. IADSA is invasive, requires skilled operators and is associated with a small but appreciable mortality and morbidity, especially in acute ICH (12). Selecting which ICH patients have a sufficiently high likelihood of a macrovascular cause to recommend IADSA is a common and important clinical question. Current practice varies widely (13): typically, the presence of pre-ICH hypertension, deep location of ICH and age are used as indicators of SVD to select patients unlikely to require IADSA(13), but the evidence supporting this is scant and often conflicting (14-16). A scoring system developed in Boston incorporating pre-ICH hypertension and age (among other factors) to identify patients at risk of a macrovascular cause has been previously validated, but did not include neuroimaging markers of SVD and only had moderate discrimination outside of the United States. (231, 232). SVD can be directly identified on brain imaging by leukoaraiosis and lacunar infarction, even on plain CT. We therefore hypothesised that, in acute ICH patients, visualization of SVD will predict a low yield of a macrovascular cause; furthermore, we aimed to develop and internally validate an algorithm to help clinicians identify patients at high risk of having a macrovascular cause underlying acute spontaneous ICH

6.2 Methods

6.2.1 Patient selection

We retrospectively reviewed all consecutive patients who underwent IADSA (the reference standard for detecting a macrovascular cause of ICH) for the investigation of ICH from January 2010-April 2014. Inclusion criteria were: acute, symptomatic, non-traumatic (spontaneous) ICH, with availability of diagnostic quality CTA, non-contrast CT and an IADSA. Patients with a primary diagnosis of subarachnoid haemorrhage (SAH) or subdural haemorrhage were excluded. In our centre, all patients presenting to our stroke unit with acute ICH have acute non-contrast CT and CTA unless there is a contra-indication. The need for an IADSA is decided during a weekly multidisciplinary vascular neuroradiological meeting where the patient's age, ICH location and history (including hypertension) are considered, as per standard clinical practice. We did not exclude patients based on age. We recorded whether the patient had a suspicion of a macrovascular cause on the non-invasive imaging prior to the IADSA to explore partial verification bias.

6.2.2 Data collection

Variables collected were: age (dichotimised into aged 45 years or over vs. under 45, in keeping with current clinical practice and previous studies (15, 233)); pre- ICH hypertension (defined by previously documented HTN for which either lifestyle advice or antihypertensive medication had been provided); and location of the ICH (cerebellar, intraventricular (pure), lobar and deep perforator territory (brainstem and basal ganglia)).

6.2.3 Image analysis

A trained vascular neuroradiology fellow (AO) reviewed the acute CTA, blinded to the IADSA result, for the presence of any structural macrovascular cause. This CTA evaluation was then compared to the final clinical report (by an accredited consultant vascular neuroradiologist). Disagreement was reviewed by a professor of vascular neuroradiology (HRJ) and a consensus decision was reached. A "negative" CTA was defined as showing no indication of a macrovascular cause. A "positive" CTA was defined by the final neuroradiology assessment as being suspicious for a macrovascular cause (graded as either having a "possible" or "definite" underlying macrovascular

cause). A clinical research fellow (DW) trained in SVD rating rated the non-contrast CT for SVD using the simplified Fazekas scale (217) and the presence of lacunae, blinded to the IADSA result. SVD on CT was dichotomised into moderate-severe (Fazekas grade ≥2 in either periventricular or deep white matter distribution) and/or the presence of any lacunar infarction vs. mild/none SVD and no lacunar infarctions. SVD was rated in the hemisphere contralateral to the symptomatic ICH to avoid misclassification of peri-haematomal oedema. Haematoma location was classified using a recently published rating instrument (234) . The IADSA was reported by a certified consultant vascular neuroradiologist. The routine IADSA protocol for investigation of intracerebral haemorrhage at our institution includes selective catheterisation of the internal carotid, external carotid and vertebral arteries, with angiographic runs of each of these vessels in at least two projections and followed through to the venous phase.

6.2.4 Statistical analysis

Univariable odds ratios and the sensitivity and specificity (presented as ROC area under the curve) were undertaken for the following variables: age, ICH location, HTN, CTA result and SVD identification on CT against the reference standard of IADSA detected macrovascular causes.

We fitted a logistic regression model to generate risk coefficients for macrovascular causes. We checked the fit of the model by comparing the model's prediction to the observed outcomes. This model was then internally validated using bootstrap validation with 1000 samples. Discrimination was quantified using the ROC area and calibration was assessed using the Cox-Miller calibration slope.

All analyses were performed using STATA 12.0 (StataCorp LP, TX).

The study was conducted and reported according to reference standards described in the TRIPOD guidelines (https://www.equator-network.org/reporting-guidelines/tripod-statement/)

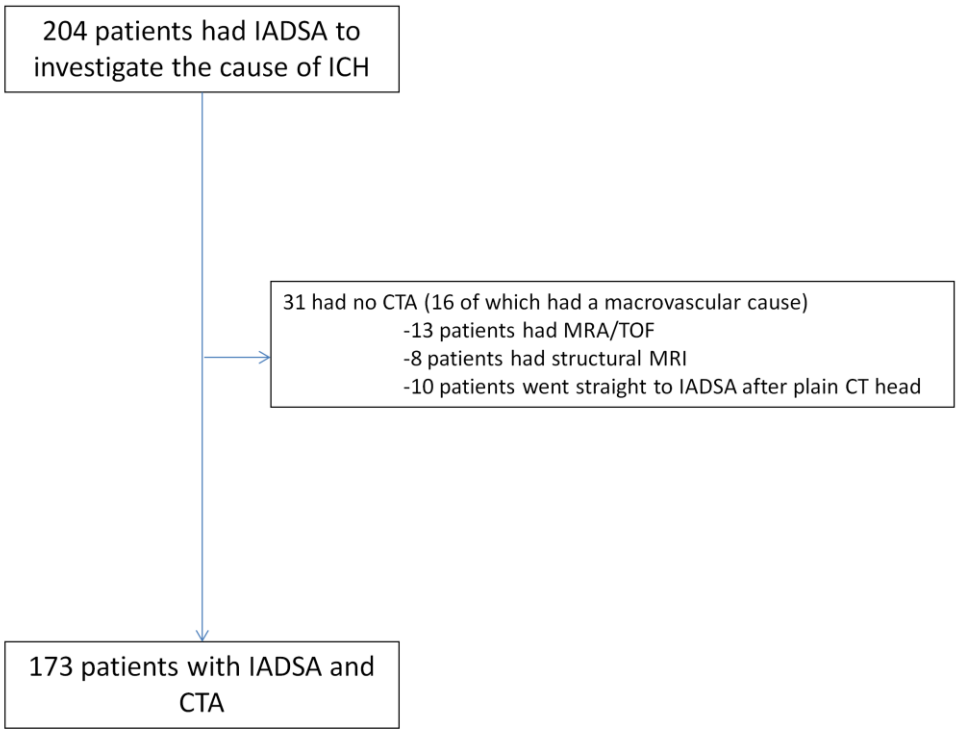
6.2.5 Ethical approval

The study was approved by the Clinical Governance Committee of the National Hospital and the UCL Institute of Neurology and National Hospital Joint Research Ethics Committee.

6.3 Results

We identified 204 patients with acute spontaneous ICH who had an IADSA. The median age was 49 (range 18 – 86, IQR 40 to 59)) and 54% were males. After quality assurance, we included 173 patients with diagnostic quality CTA in the study (figure 17).

Figure 17 Flow chart showing patient selection



Within this group there were 78 IADSA-defined macrovascular causes (68 AVMs, 7 dural fistulas, 2 aneurysms and 1 carotid-cavernous fistula). The median CTA to IADSA time was 2 days (IQR 1 to 11). 3 vascular malformations were only detected on repeat IADSA; of these patients the median CT-repeat DSA was 264 days (IQR 78 to 314). ICH locations in the final cohort were: lobar 83, deep perforator territory 60 (basal ganglia, thalamus, caudate, brainstem), Cerebellar 21, pure intraventricular: 9. (Table 11).

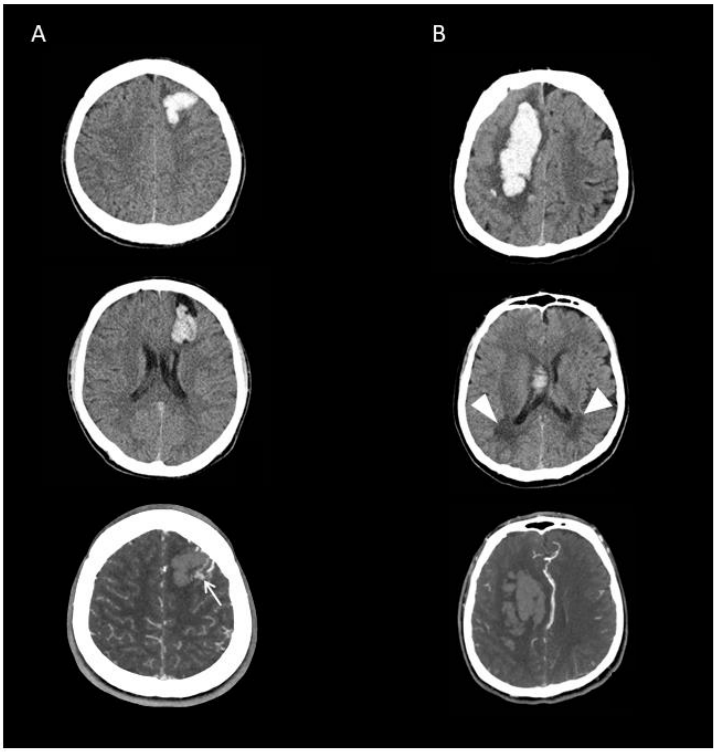
Table 11 Characteristics of patients in study

Variable	Entire cohort (n=173)
Age, years, median (IQR) [Range]	49 (40 to 59) [18 to 86]
Gender, Female n (%)	80 (46)
Pre- ICH HTN n (%)	52 (30)
CTA to IADSA, Days, median (IQR)	2 (1 to 11)
Abnormal CTA, n (%)	71 (41)
Confluent leukoaraiosis on CT, n (%)	41 (24)
Lacunar infarcts on CT, n (%)	13 (8)
Any SVD on CT, n (%)	47 (27)
Location of ICH: Cerebellar, n (%)	21 (12)
Location of ICH: Deep perforator territory, n (%)*	60 (35)
Location of ICH: Pure intraventricular, n (%)	9 (5)
Location of ICH: Lobar, n (%)	83 (48)

CTA identified 85 cases with a definite or possible macrovascular cause. 67/67 cases identified as “definite” vascular abnormalities on CTA were identified as true macrovascular causes on IADSA. 11/18 cases identified as “possible” macrovascular causes on CTA were identified as true macrovascular causes on IADSA. In 17 instances there was discordance between the trained vascular neuroradiology fellow and the clinical report; 11 of these were judged to have a possible macrovascular cause by consensus adjudication with the professor of vascular neuroradiology (HRJ).

In univariable analysis a positive CTA (“definite” or “possible” suspicion for a macrovascular cause) has the highest odds ratio for detecting a macrovascular cause (and the greatest area under the curve), followed by: non-deep perforator ICH location; the absence of SVD; the absence of pre-ICH hypertension; and age less than 45 years. (Table 12) (Figure 18).

Figure 18 Imaging examples of patients with and without high grade leukoaraiosis on plain CT



A) Left frontal lobar intracerebral haemorrhage. No evidence of leukoaraiosis. An arterio-venous malformation is shown on CTA source data (AVM nidus white arrow).

B) Right fronto-parietal lobar intracerebral haemorrhage extending down to the corpus callusum. Evidence of confluent leukoaraiosis in the peritrigonal white matter bilaterally (arrow heads). The CTA a source data show displacement of the anterior cerebral arteries across the midline. There area of haemorrhage is hypovascular and there is no evidence of a vascular malformation

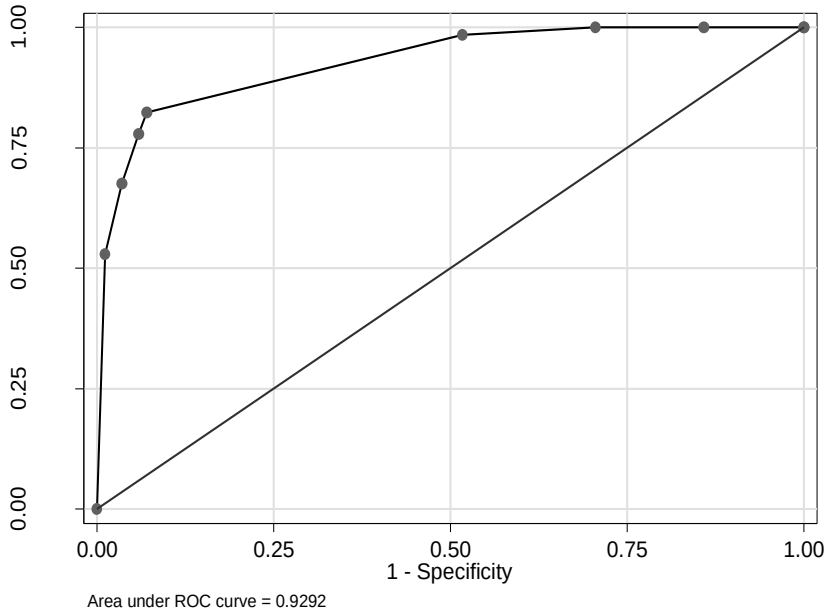
Table 12 Univariable Odds ratio and area under the curve for selected variables sued in identifying a macrovascular cause

Predictor variable		OR (95% CI)	ROC AUC (95% CI)
CTA positive* for vascular malformation		57.5 (21.9 to 150.5)	0.87 (0.82 to 0.92)
ICH location			0.66 (0.59 to 0.74)
	deep perforator territory	1 (ref)	
	cerebellar	4.4 (1.5 to 12.5)	
	pure intraventricular	6.6 (1.5 to 29.7)	
	lobar	4.1 (2.0 to 8.5)	
Absence of confluent SVD on CT		3.2 (1.5 to 6.7)	0.61 (0.54 to 0.67)
No pre-ICH hypertension		2.4 (1.2 to 4.7)	0.59 (0.52 to 0.65)
Age <45 years		1.3 (0.7 to 2.4)	0.53 (0.46 to 0.61)

Part 3: Intracerebral haemorrhage populations

We fitted a logistic regression model to the five predictors (with ICH location simplified to non-deep perforator ICH location vs. deep perforator ICH location) to develop a model to predict the risk of a macrovascular cause. Abnormal CTA was the most important predictive factor of the presence of a macrovascular cause in the model (OR 67.4; 95% CI 21.3 to 213.1 p<0.001), followed by absence of SVD (OR 5.0; 95% CI 1.3 to 19.6 p=0.019); and absence of pre-ICH hypertension (OR 3.4; 95% CI 1.0 to 11.4 p=0.05). The two weakest predictors -ICH location (OR 2.8; 95% CI 0.96 to 8.5 p=0.060) and age <45y (OR 1.1; 95% CI 0.4 to 3.1 p=0.90) - were then omitted, which had little impact on the model fit. This simplified model contains just 3 binary predictors (regression coefficients and model intercept: CTA positive 4.7, No SVD 1.5, No pre- stroke hypertension 1.3, intercept -4.0), and thus can make 8 unique predictions. which showed excellent agreement with the actual patient IADSA findings (Hosmer-Lemeshow goodness of fit p=0.99; no evidence of lack of fit) (Table 13). Bootstrap validation reveals that the 'optimism-adjusted' (235) ROC area for the simplified model is 0.919 (Figure 19) and that the Cox-Miller calibration (235) slope is 0.949 which suggests that the risk model is well calibrated.

Figure 19 ROC curve for our model with only 3 predictors used to identify a macrovascular cause in ICH



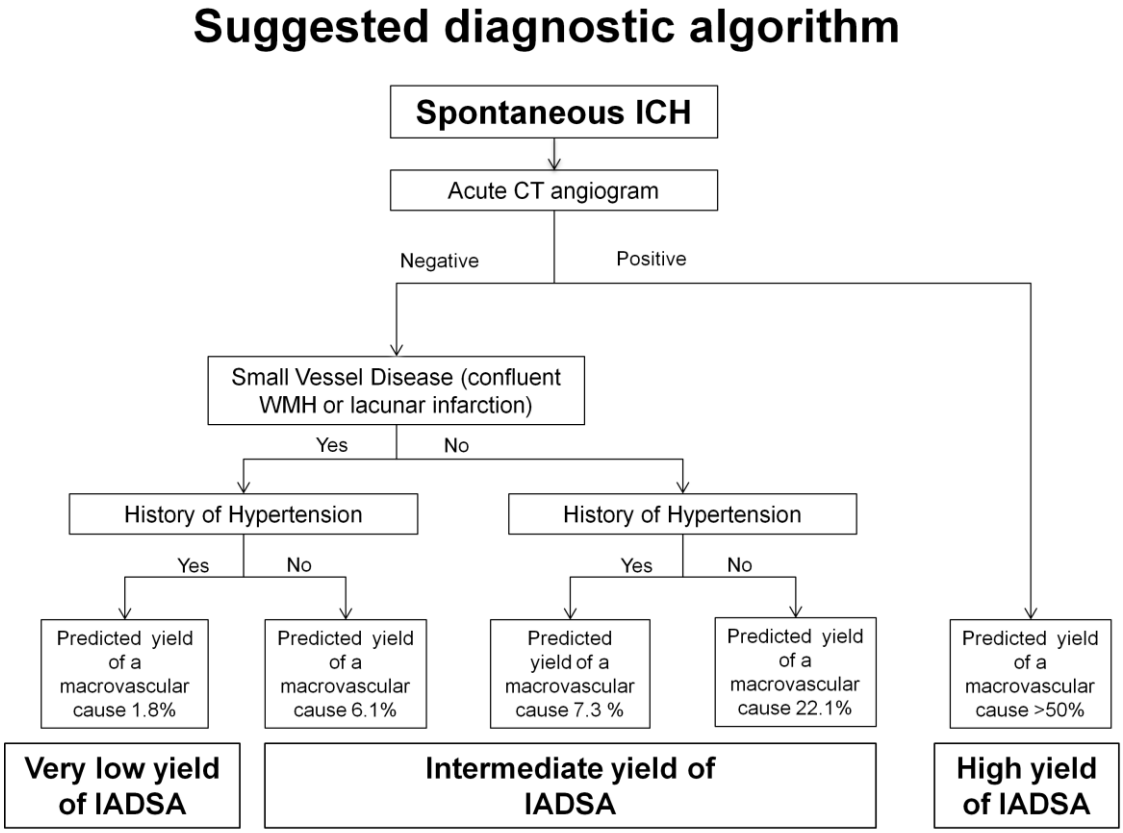
The final model allowed us to estimate the risk of a macrovascular cause for any patient based on the combination of CTA result, pre-ICH hypertension and SVD on CT. (Table 13). The predicted yield of a macrovascular cause for each combination of predictors is also presented in an algorithm (Figure 20).

Table 13 Yield of intracranial macrovascular causes from the optimised model compared to the actual yield

Predictors			Observed proportion of patients with a macrovascular cause for each combination of predictors in our dataset, % (95% CI) [raw numbers]	Model predicted proportion of patients with a macrovascular cause for each combination of predictors, %
CTA result	SVD on CT	HTN		
Positive	No	No	95.3% (84.2 to 99.4) [41/43]	95.8%
Positive	No	Yes	85.7% (57.2 to 98.2) [12/14]	86.4%
Positive	Yes	No	80.0% (44.4 to 97.4) [8/10]	83.7%
Positive	Yes	Yes	75.0% (19.4 to 99.4) [3/4]	59.0%
Negative	No	No	23.1% (12.5 to 36.8) [12/52]	22.1%
Negative	No	Yes	5.9%(0.1 to 28.7) [1/17]	7.3%
Negative	Yes	No	6.3 % (0.2 to 30.2) [1/16]	6.1%
Negative	Yes	Yes	0% [0/17]	1.8%

Footnote: SVD. Small vessel disease. “Positive” includes CTA showing a “definite” or “possible” macrovascular cause; “negative” denotes CTA showing no suspicion of a vascular malformation.

Figure 20 Suggested diagnostic algorithm



6.4 Discussion

In a population of acute ICH patients at risk of an underlying macrovascular cause (having had IADSA based on age, ICH location and vascular risk factors), the presence of small vessel disease (confluent leukoaraiosis and/or one or more lacunes) on non-contrast CT is a useful predictor of the likelihood of finding an underlying macrovascular cause. In our internally validated model, an abnormal CTA, or the combination of a normal CTA with no evidence of SVD (confluent leukoaraiosis on CT) indicate an intermediate to high yield of an underlying macrovascular cause, which might justify undertaking IADSA.

If externally validated on a prospective cohort, the use of our algorithm in clinical practice could lead to more macrovascular causes being detected (higher sensitivity) with an acceptable level of non-diagnostic IADSAs. For instance, if we used our algorithm on our own sample, choosing a predicted yield for a macrovascular cause of >5% as an indication for IADSA, our algorithm would yield 12 more macrovascular causes compared to using CTA alone, at the expense of 85 more negative IADSAs (i.e. an extra 7 patients undertaking an IADSA per additional macrovascular cause identified). In practice, clinicians must balance the expected yield of the IADSA against the procedural risk.

The sensitivity of acutely performed CTA for identifying a macrovascular cause in our study (82%) is lower than reported in a recent meta-analysis of 95% (CI 90-97%) (236), likely due to our use of repeat or delayed IADSA, which revealed a macrovascular cause not seen on the acute IADSA in 3 instances. Delayed IADSAs were not undertaken in studies involved in the above meta-analysis. Previous studies compared only acute CTA to acute IADSA. However, a recent multicentre prospective study also found a lower sensitivity of acute CTA, in line with our findings (237). The difference is consistent with an additional yield of macrovascular causes from delayed IADSA, a well-recognized observation in clinical practice, which could be in part related to acute haemorrhage and perihaematomal oedema obscuring small macrovascular lesions. Our study was not able to investigate whether delayed CTA has similar diagnostic accuracy to delayed IADSA, which is a topic for further research.

Although a small case series has previously shown the added diagnostic value of MRI when IADSA is inconclusive (238), we are only aware of one other study that specifically tests direct visualization of small vessel disease to improve the prediction of the likelihood of an underlying vascular malformation (237). In keeping with this study (237), our data

suggests the presence of SVD on acute CT (when CTA is not suspicious for a macrovascular cause) is a useful predictor of a low yield of an underlying macrovascular cause in the investigation of younger patients with spontaneous ICH (mean ages 53 years in the previous study (237) and 49 years in the current study).

Importantly, in our study 3 patients with an underlying macrovascular cause were older than 45 years with known hypertension and a cerebellar ICH. This combination of variables has previously been associated with a 0% yield of macrovascular causes (15), but our data indicate that further investigation looking for a macrovascular cause should be considered in this clinical situation.

Our study has important strengths. All patients identified with a suspected macrovascular cause for ICH at our centre undergo IADSA, so our initial search captured all patients diagnosed with a known macrovascular cause over the study period. Most patients had acute CTA on admission using a standardised care pathway, reducing the potential for selection bias. Our centre has a low threshold for requesting IADSA in suspected macrovascular causes and we were therefore able to include a large cohort of patients with CTA, CT and IADSA (n=173), which compares favourably in size to previous studies (233, 239-242). The time interval between CTA and the initial DSA was very short, and we included independent blinded CTA ratings by vascular neuroradiologists. Furthermore, we performed delayed and multiple IADSAs in selected patients, which increased the detection of macrovascular causes.

Nevertheless, our study also has limitations. The retrospective nature of the study is likely to cause selection and partial verification bias. Although 63% of our cohort had a normal initial CTA (suggesting that there is little partial verification or “work up” bias), our sample is younger than an unselected ICH cohort (median age 49, IQR 40-59), suggesting selection bias, likely because IADSA was an inclusion criterion. This reflects current clinical practice with an inherent hesitancy for requesting IADSA in older individuals (e.g. > 70 years) in whom that the yield of a macrovascular cause is perceived to be very low (15). This selection bias toward younger individuals also explains why our proportion of vascular malformations is much higher than one would expect from an unselected population. Our results can thus only be generalized to younger patients with ICH. This is a difficult bias to overcome in any study, because undertaking IADSA in all unselected consecutive patients

with ICH is unlikely to be considered ethical because of the procedural risk, which may be as high as 3% in ICH (12). Nevertheless, this acknowledged selection bias is unlikely to weaken our main finding that SVD is predictive of a low yield of a macrovascular abnormality.

We did not capture ICH volume in our cohort, which would have been useful to better characterise our population. The proportion of patients with larger ICH might be relevant, because such patients are less likely to undergo acute IADSA, and can be difficult to classify according to anatomical ICH location. We did not include any patients with multiple acute haemorrhages, presumably because they were considered unlikely to have multiple macrovascular causes and thus did not undergo an IADSA at our centre. Despite these limitations, the demographic features of our study suggest that it is likely to be generalizable to the ICH population that in clinical practice is considered for investigation for an underlying macrovascular cause. A further limitation is that we did not routinely undertake MRI in all included patients, and were therefore unable to investigate additional markers of cerebral SVD underlying ICH, such as cerebral microbleeds, dilated perivascular spaces or cerebral atrophy (89, 93). The use of standardised MRI prior to IADSA would have strengthened our study as it is better able to differentiate between the type of SVD (i.e. cerebral amyloid angiopathy or hypertensive arteriopathy), and is superior for the detection of other underlying causes for ICH (e.g. cavernomas or mass lesions). However, the lack of MRI is unlikely to have compromised our ability to detect leukoaraiosis, the main SVD feature analysed in our study: a previous study (243) demonstrated that although MRI is more sensitive than CT in detecting subtle (Fazekas grade 1) white matter lesions, MRI and CT have a high concordance in detecting clinically more relevant Fazekas grade 2 and 3 lesions, which we used as predictor in our analysis. Our choice of CT (which was available in all patients acutely at the time of haemorrhage) for assessment of white matter lesions is therefore very unlikely to have led to a significant underestimation of moderate- severe (Fazekas grade ≥ 2) small vessel disease. Furthermore, our (unpublished) internal inter-rater reliability is moderate to good for the identification of Fazekas 2/3 in ICH populations (Kappa = 0.60), and we were careful to exclude perihaematomal oedema as a potential mimic of small vessel disease by assessing hemisphere contralateral to the ICH. We did not encounter any cases of transependymal

oedema due to acute hydrocephalus, likely due to the selection bias of our patients where we only included those with IADSA, an intervention unlikely to be undertaken in such patients. By contrast, the poor sensitivity and specificity (especially with regards to differentiating enlarged perivascular spaces) of identifying lacunar infarction on CT remains a limitation.

In summary, we show, in a younger acute ICH population (median age 49 years) at risk of having an underlying macrovascular cause, the identification of SVD (moderately severe leukoaraiosis or lacunar infarction on CT), in combination with CTA and pre-ICH hypertension ICH, can predict which ICH patients have a low yield of an intracranial macrovascular cause. If externally validated, our algorithm has potential to more effectively target invasive IADSA towards patients with the highest potential diagnostic yield, avoiding unnecessary invasive tests and improving the diagnostic pathway for patients with spontaneous ICH.

7.0 Risk of recurrent intracerebral haemorrhage and ischaemic stroke after intracerebral haemorrhage: multicentre prospective cohort study

Introduction Survivors of intracerebral haemorrhage (ICH) are at risk of both recurrent ICH and ischæmic stroke (IS), leading to uncertainty concerning the benefits and risks of treatment with antithrombotic drugs. ICH location (lobar vs deep) might influence the risk for recurrent ICH and IS, but data are limited.

Methods We included data from participants with ICH in a prospective multicentre observational study and investigated the incidence of IS and recurrent ICH, according to index ICH location (lobar vs. non-lobar (basal ganglia, thalamic, or brainstem, but not cerebellar).

Results We included 1094 patients, mean age 73 years (SD 12 years); 447 (43%) ICH were lobar, and 581 (57%) were non-lobar. 60 patients had 35 ICH events over 1648 patient-years of follow up and 27 IS events over 1608 patient-years of follow-up. Lobar ICH location was independently associated with a higher rate and risk of recurrent ICH compared to non-lobar ICH (3.6%/year vs. 1.1% per year; adjusted HR 3.25, 95% CI 1.49 to 7.06, respectively). Lobar ICH location was associated with a lower rate of IS compared to non-lobar ICH (0.9%/year vs 2.0%/year) but the adjusted risk was not statistically significant (adjusted HR 0.40, 95% CI 0.16 to 1.01).

Conclusions Lobar ICH survivors have a higher rate and risk of recurrent ICH than non-lobar ICH survivors. Whilst they also have a lower rate of new IS, the risk was not significantly different in adjusted analyses. Further studies are needed to define whether treatment effects (e.g. antithrombotic drugs for IS prevention) differ according to ICH location.

7.1 Rationale for study

Intracerebral haemorrhage (ICH) is a devastating condition with mortality over 50% at 1 year(3). A difficult clinical dilemma in ICH survivors is whether to recommend antithrombotic treatments that could reduce future vaso-occlusive ischaemic events, including acute ischaemic stroke (IS), but might increase their future risk of ICH. This is a pertinent question for patients with an indication for preventive treatments including antiplatelet agents (e.g. in patients with ischaemic heart disease), anticoagulants (e.g. in patients with atrial fibrillation (AF))(244), or statins (245-248), all of which might increase recurrent ICH risk. Identifying clinical and imaging risk factors associated with IS and recurrent ICH could help clinicians with these decisions. Whilst there is some data on the risk of recurrent ICH (estimated between 1.3% and 7.4% annually(3)), which might be highest for patients with lobar ICH(3), there is less data on the risk of subsequent IS and associated risk factors(3, 124-126). Further data on the risks of IS and recurrent ICH, as well as their clinical and imaging associations, should help guide clinical decision-making after ICH, especially regarding antithrombotic (antiplatelet and anticoagulant) drugs.

This study, therefore, investigated the incidence and the demographic, clinical and neuroimaging associations of stroke events (both IS and recurrent ICH) in ICH survivors, using data from a prospective multicentre UK cohort study of adults with neuroimaging confirmed spontaneous primary ICH. We hypothesized that participants with lobar ICH would have a higher risk of recurrent ICH and a lower risk of IS than those with non-lobar ICH.

7.2 Methods

7.2.1 Clinical data

All data were collected as part of CROMIS-2 ICH (NCT02513316), a prospective multicentre observational study of adult ICH survivors; full details of the study protocol have been published elsewhere (208). Variables of interest for all univariable analyses were pre-specified for both IS and recurrent ICH.

7.2.2 Clinical outcomes during follow-up

Our outcome events of interest were recurrent ICH or IS. Follow up was collected from patients and GPs via a questionnaire, nominally at 6 months. National Health Service information centre data was reviewed to ensure there were no patient admissions not captured by the patient or GP questionnaire. Primary events were not adjudicated centrally. Primary events (recurrent ICH or new IS) were diagnosed if the patient was hospitalized, underwent brain imaging and given a diagnosis of either ischaemic stroke or recurrent ICH by the local investigators

7.2.3 Imaging data

Baseline brain imaging (acute CT scans or acute MRI) were acquired as part of standard care, mainly at hospital admission. Scans were rated for leukoaraiosis by a trained research fellow (DW) using a validated scale(249). Leukoaraiosis was then dichotomised into none/mild or moderate/severe based upon whether the score added to a value of >3. Lacunar infarction was rated according to STRIVE guidelines(11). A scan was “positive” for small vessel disease in the presence of either lacunar infarction or moderate/severe leukoaraiosis. Haematoma location was defined using a published scale, then subdivided into lobar or non-lobar(250).

7.2.4 Statistical analysis

All analysis was undertaken on Stata version 14.0 (StataCorp LP, TX). Baseline variables were presented as means and SD if normally distributed, median and IQR if not normally distributed and n with percentage if categorical. Cox regression analysis was undertaken

due to variable follow up. In all Cox models' patients with cerebellar ICH were excluded from analysis as it is unclear whether these patients share similar causes and prognosis with lobar or deep ICH. Univariable Cox regression was used to compare the pre-specified variables of interest. Multivariable Cox regression was then performed, due to the low number of events we adjusted for variables identified as significant ($p<0.05$) in the univariable analyses. In a sensitivity analysis, we additionally included variables significant at the 20% level one by one in turn. We assessed the assumption of proportional hazards by visual inspection of each log-log plot of survival.

7.3 Results

CROMIS-2 ICH recruited 1094 patients. (Figure 21). The mean age was 73 years (SD 12 years) and 463 (43%) were female. 372 (35%) had atrial fibrillation. 440 (41%) patients were on anticoagulation at the time of their ICH, 274 (25%) on antiplatelets and 444 (43%) on statins at the time of their ICH. When considering ICH location, 447 (41%) were lobar and 581 (53%) were deep or located in the brainstem and 65 (6%) were in the cerebellum. 1 patient's ICH location could not be determined (Table 14)

Figure 21 Study flow chart

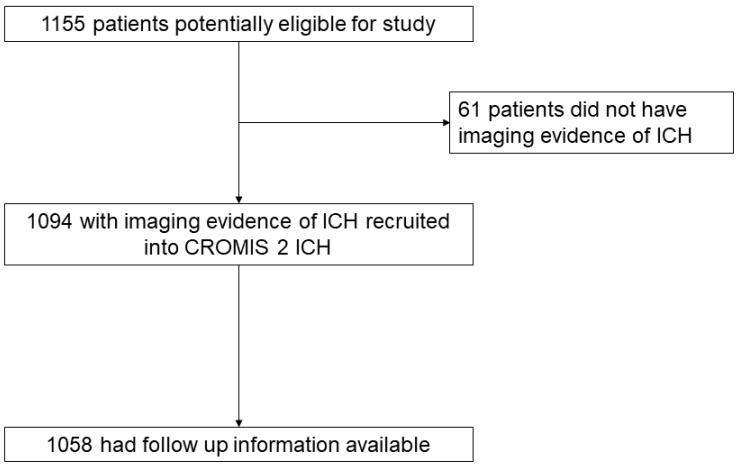


Table 14 Baseline characteristics of the study population (n=1094).

Demographic and clinical features	
Age, median (SD)	73 (12)
Sex, female n (%)	463 (43)
Hypertension, n (%)	713 (67)
Diabetes mellitus, n (%)	201 (19)
Hyperlipidaemia, n (%)	465 (44)
Atrial fibrillation, n (%)	372 (35)
Previous IE, n (%)	267 (25)
Previous ICH, n (%)	44 (4)
Vascular disease #, n (%)	193 (18)
Total cholesterol mmol/l[†], median (IQR) *available in 512	4.5 (3.7 to 5.5)
Medication at time of study entry with index ICH	
Antiplatelet use, n (%)	274 (25)
Anticoagulation use, n (%)	440 (41)
Statin use, n (%)	444 (43)
Imaging features	
SVD presence n (%)	373 (35)
ICH location, deep, n (%)	581 (53)
ICH location, lobar, n (%)	447 (41)
ICH location, cerebellar, n (%)	65 (6)
Discharge medication following index ICH	
Statin	323 (30)

Footnote
Vascular disease includes ischaemic heart disease and peripheral vascular disease

1058 (97%) patients had follow up during which 60 patients had 62 stroke events: 35 recurrent ICH events over 1648 patient-years (2.1%/year) and 27 IS events over 1608 patient-years (1.7%/year). Two patients had recurrent IS events whilst one patient had an IS followed later by a recurrent ICH.

7.3.1 Recurrent ICH rate by ICH location and risk

24 patients with lobar ICH had a recurrent ICH over 665 patient-years (3.6%/year) vs. 11 patients with non-lobar ICH over 982 patient-years, a rate of (1.1%/year)

In univariable analyses (Table 15), previous ICH, antiplatelet use at the time of index ICH, and lobar ICH were associated with recurrent ICH. In multivariable analysis (adjusting for antiplatelet use and previous ICH), lobar ICH location (HR 3.25, 95% CI 1.49 to 7.07) and previous antiplatelet use (HR 2.22, 95% CI 1.09 to 4.54) remained significantly associated with recurrent ICH risk (Table 16). The addition of further variables in a sensitivity analysis did not significantly change the result (data not shown). Kaplan-Meier curves stratified by ICH location are presented for both recurrent ICH and IS (figure 22)

Table 15: Univariable analyses for risk of a recurrent ICH following ICH

	HR	95% CI	p value
Demographics			
Age (per year increase)	1.02	0.99 to 1.05	0.120
Sex (female)	1.36	0.69 to 2.66	0.371
Hypertension (presence)	1.43	0.67 to 3.06	0.360
Diabetes mellitus(presence)	1.50	0.70 to 3.21	0.291
Hyperlipidaemia (presence)	0.99	0.49 to 1.99	0.972
Atrial fibrillation (presence)	0.85	0.41 to 1.77	0.659
Previous stroke or TIA (presence)	1.66	0.82 to 3.33	0.157
Previous ICH (presence)	3.46	1.22 to 9.86	0.020
Medications at admission			
Antiplatelet use at the time of baseline ICH	2.16	1.12 to 4.27	0.022
Anticoagulation use at the time of baseline ICH	0.93	0.47 to 1.85	0.836
Statin use at the time of baseline ICH	1.22	0.62 to 2.40	0.561
Imaging findings			
SVD presence	1.62	0.83 to 3.15	0.155
ICH location, lobar (vs. non-lobar ICH location excluding cerebellar ICH)	3.57	1.66 to 7.68	0.001
Medications at discharge			
Statin	1.33	0.67 to 2.66	0.420

Key: ischaemic stroke-ischaemic stroke, TIA-transient ischaemic attack, ICH intracerebral haemorrhage, SVD-small vessel disease.
* Vascular disease incorporates ischaemic heart disease and peripheral vascular disease

Table 16 Multivariable analysis for risk of a recurrent ICH following ICH

Covariate	**HR**	**95% CI**	**p value**
Lobar ICH location (vs. non-lobar ICH location excluding cerebellar ICH)	3.25	1.49 to 7.06	0.003
Previous ICH	2.66	0.80 to 8.80	0.109
Antiplatelet at time of baseline ICH	2.22	1.09 to 4.54	0.029

Key: ICH: Intracerebral haemorrhage, TIA –transient ischaemic attack

7.3.2 New IS rate by ICH location and risk

6 patients with lobar ICH location had a new IS over 654 patient-years of follow-up, (0.9% per year) vs. 19 patients with non-lobar ICH over 953 patient-years of follow-up (2.0% per year).

Univariable analyses of baseline associations with the risk of IS following ICH are shown in Table 17. Only the presence of atrial fibrillation and anticoagulant use at baseline ICH had a significant association with new IS. In multivariable analysis adjusting for AF at the time of index ICH and previous IS or TIA, only atrial fibrillation presence at time of baseline ICH remained significantly associated with IS occurrence (HR 2.59; 95% CI 1.13 to 5.92 p=0.025). Lobar ICH location remained inversely associated with IS occurrence but this was not statistically significant (HR 0.40; 95% CI 0.16 to 1.02 p=0.055). (Table 18). Anticoagulation at time of ICH was not entered into the model due to collinearity with AF. Sensitivity analysis did not significantly change the result (not shown).

Table 17 Univariable analyses for risk of new ischaemic stroke

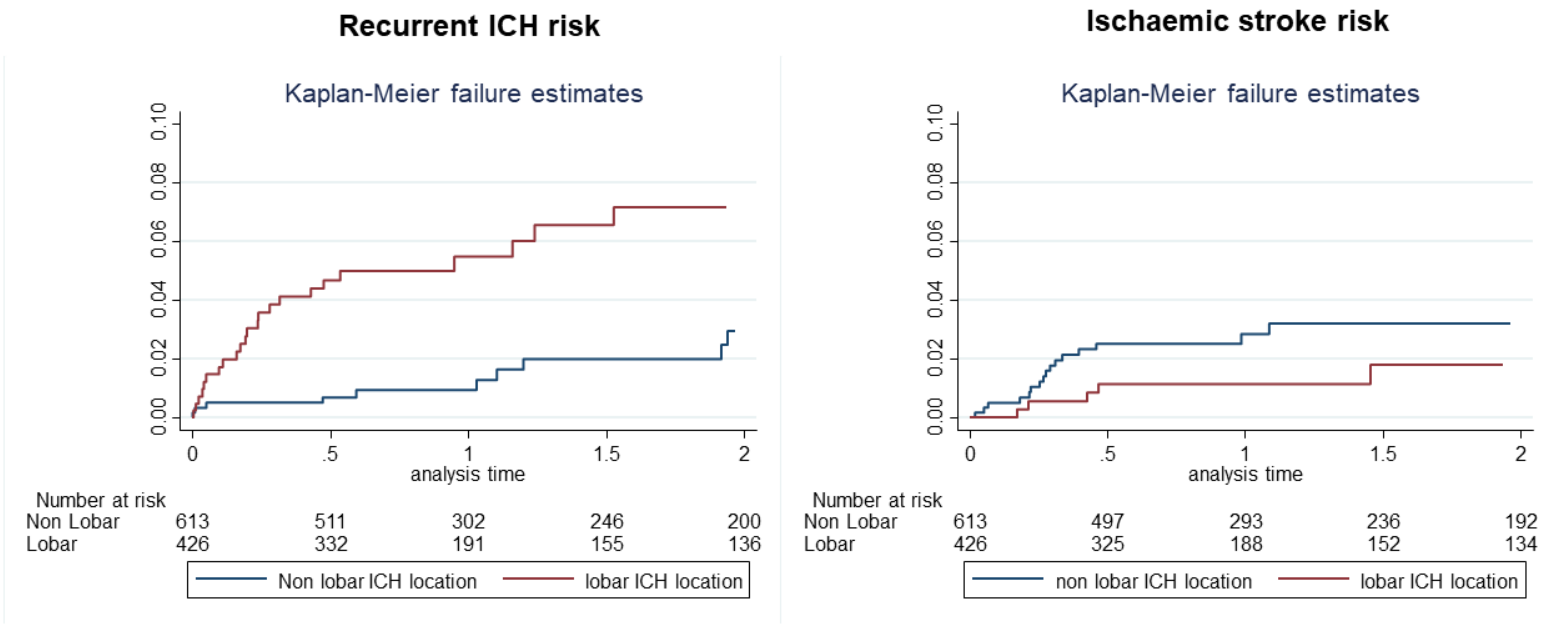
	HR	95% CI	p value
Demographics			
Age (per year increase)	1.02	0.98 to 1.05	0.289
Sex (female)	0.90	0.40 to 2.00	0.798
Hypertension (presence)	0.73	0.33 to 1.65	0.457
Diabetes mellitus(presence)	1.19	0.44 to 3.19	0.728
Hyperlipidaemia (presence)	1.31	0.59 to 2.93	0.503
Atrial fibrillation (presence)	2.78	1.26 to 6.12	0.011
Vascular disease *(presence)	1.24	0.46 to 3.30	0.670
Previous stroke or TIA (presence)	2.21	0.99 to 4.93	0.052
Previous ICH (presence)	1.07	0.15 to 7.95	0.943
Medication at admission			
Antiplatelet use	0.74	0.30 to 1.98	0.554
Anticoagulation use	3.43	1.48 to 7.95	0.004
Statin use	1.54	0.70 to 3.38	0.279
Imaging findings			
SVD presence	2.13	0.97 to 4.67	0.059
ICH location lobar (vs. non-lobar ICH location excluding cerebellar ICH)	0.44	0.18 to 1.12	0.084
Medications at discharge			
Statin	0.69	0.28 to 1.73	0.427

Table footnote
TIA-transient ischaemic attack, ICH intracerebral haemorrhage, SVD-small vessel disease.

Table 18 Multivariable analysis for risk of an ischaemic event following ICH

Covariate	**HR**	**95% CI**	**p value**
Lobar location of ICH (vs. non-lobar ICH location excluding cerebellar ICH)	0.40	0.16 to 1.01	0.055
Previous stroke or TIA	1.65	0.70 to 3.87	0.248
Atrial fibrillation	2.59	1.13 to 5.92	0.025

Figure 22 Kaplan Meier failure estimates based upon ICH location for recurrent ICH and incident IS.



Given the low numbers of patients who started or restarted antiplatelet and anticoagulant medications at discharge and lack of data on whether these medications were continued or restarted during follow up, we could not explore their impact on recurrent ICH or new ischaemic stroke. Statin use at hospital discharge was not associated with incident IS or recurrent ICH during follow-up (Univariable HR 1.33; 95% CI 0.67 to 2.66 and univariable HR 0.68; 95% CI 0.28 to 1.73 respectively).

7.4 Discussion

We show that, in ICH survivors overall, the rates of recurrent ICH and new IS are similar, at 2.1% per year and 1.7% per year, respectively. However, patients with baseline lobar ICH have approximately three times the rate risk of recurrent ICH compared to those with non-lobar ICH. Taking an antiplatelet agent at the time of ICH and having a previous ICH were independent risks for recurrent ICH, while AF at the time of ICH was the only independent risk for new IS.

In keeping with previous studies we confirm that in ICH survivors overall, the risk of ischaemic stroke is similar to that of recurrent ICH(251, 252) while lobar ICH location is a risk factor for recurrent ICH(252, 253). However, our study also suggests that lobar ICH is associated not only with a higher risk of recurrent ICH, but also a lower risk of IS.

Our findings have potential clinical implications regarding antithrombotic decisions in ICH survivors. Although registry data suggests in patients with AF, restarting anticoagulation is safe, most of the published studies could not account for the effect of ICH location(254, 255). Moreover, randomised trial data are lacking for the use of both anticoagulants and antiplatelets after ICH. Our data suggest that the effects of antithrombotics in ICH survivors might differ according to the location of the index ICH and that ICH location should be considered in ongoing trials (APACHE-AF (NCT02565693), SoSTART (NCT03153150), PRESTIGE AF) on this question.

We could not explore the association between antithrombotic use at hospital discharge and outcome events as the prevalence of antithrombotic use at discharge was very low and we do not have information on whether these medications were started or discontinued during follow up.

Statin use on discharge was not associated with either recurrent ICH or new IS. Statin use after ICH has been a topic of discussion since the SPARCL trial where patients with ICH as an entry into the trial who started on statins had over 5 times risk of recurrent ICH than those who were not (256). This was, however, only based on 93 patients and 9 events, 7 of which were in the statin arm. Following this result, single centre registries (257) and case-

control studies (258, 259) with much larger numbers of patients with ICH have failed to replicate this finding.

Recurrent ICH was associated with antiplatelet use but not anticoagulation use at admission with ICH. However, this association could be due to confounding by the indication for taking an antiplatelet drug: antiplatelet use was over-represented in those with previous stroke or TIA, those with vascular disease, and in those with hypertension (results not shown). Thus, it is possible that antiplatelet use is an indication of 'vascular disease' (including small vessel disease), which might increase the risk of recurrent ICH rather than the antiplatelet medication itself. Due to the small number of events we were unable to explore this further by adjusting for potential indications for antiplatelet drug use.

Our study has strengths; we included a large multi-centre cohort of ICH survivors from around the UK, increasing the generalizability of our findings. Where possible we undertook multivariable regression to account for differences in patient demographics and risk factors. This study also benefits from the detailed clinical and neuroimaging phenotyping undertaken at baseline.

We also acknowledge limitations: our observational study is biased toward ICH survivors, although this is the patient group in which treatment decisions to prevent future events is most important. There were limited ICH and IS events during follow up, which limits our ability to run a robust multivariable analysis. We only have information with regard anticoagulation at discharge or at an event, but did not collect this information at routine six-month follow up. Therefore, we were not able to explore how restarting antithrombotics in those with an indication modulated the outcome events. A further limitation is only a small subset underwent MRI to evaluate other relevant markers of small vessel disease that are not visible on CT (for example cerebral microbleeds).

Our findings of different risks of recurrent ICH and IS according to ICH location suggest that for secondary prevention strategies after ICH (including the use of antithrombotic drugs), the location of the ICH should be considered. Our findings are also relevant for

randomised controlled trials in ICH survivors with an indication for anticoagulation and antiplatelets are awaited.

8.0 Validating CHA_2DS_2-VASc in patients with intracerebral haemorrhage and atrial fibrillation

Introduction: The CHA_2DS_2-VASc score (Congestive heart failure, Hypertension, Age, Diabetes, Stroke, Vascular disease, Sex) has been validated in different atrial fibrillation (AF) patient populations, but not in patients who have had intracerebral haemorrhage (ICH). This study aims to validate the CHA_2DS_2-VASc risk prediction system in patients with ICH.

Methods: We included data from a prospective observational multicentre study of patients with imaging-confirmed ICH and documented AF. CHA_2DS_2-VASc scores were generated for each patient. ROC curves, Hosmer-Lemeshow tests and corresponding risk estimates comparing subsequent ischaemic stroke events against the CHA_2DS_2-VASc risk estimates were then derived. The observed and predicted risks were then plotted against each other for a visual approximation of fit. We tested the calibration of the CHA_2DS_2-VASc score by fitting a logistic regression model with ischaemic stroke as the outcome and the predicted log-odds of ischaemic stroke (from CHA_2DS_2-VASc) as the only predictor.

Results: 322 patients were included in the final analysis. There were 17 ischaemic strokes and 7 major bleeding events (all recurrent ICH) within a median follow up period of 228 days (IQR 186 to 420). The median CHA_2DS_2-VASc score was 4 (IQR 3 to 5). Compared to the risk predictions adapted from CHADSVASC.org our findings showed excellent agreement (Hosmer-Lemeshow goodness of fit: p=0.85). The calibration was also satisfactory (slope 1.02 and intercept 0.21, p=0.80), with no evidence of a difference. The C statistic was 0.64.

Conclusion: The CHA_2DS_2-VASc scoring system has similar predictive value in ICH survivors with AF compared to other AF populations, so might be useful in estimating the risk of ischaemic stroke in this population.

8.1 Rationale for study

The CHA_2DS_2-VASc score is a commonly used and validated risk prediction system that helps clinicians with anticoagulant decisions regarding ischaemic stroke risk in patients with atrial fibrillation (AF) (260-262). It has been validated in population-based samples (261, 263, 264), patients with ischaemic stroke(265), renal failure(266) or post-myocardial infarction(267) as well as in populations of different ethnicity(263, 268). However, CHA_2DS_2-VASc has not been validated in patients with intracerebral haemorrhage (ICH) and AF; the Euro Heart Survey on AF (260) from which CHA_2DS_2-VASc was devised included only 62 patients with a history of major bleeding, whilst the validation cohort excluded patients with ICH(264).

AF is common in patients with ICH(244), and leads to challenging antithrombotic decisions because of concerns about the risk of recurrent ICH as well that of ischaemic stroke(3); moreover, anticoagulants result in poorer outcomes should ICH occur(251, 252). Data from recent large observational trials suggest that restarting anticoagulation is associated with decreased risks of ischaemic stroke mortality, without an increase in ICH events(129, 244, 254). However, these studies could not investigate risks at an individual patient level. If the CHA_2DS_2-VASc score can help predict the risk of ischaemic stroke in ICH patients with AF, this could help clinicians judge the potential benefits and risks of anticoagulation in individual patients.

This study, therefore, aimed to validate the CHA_2DS_2-VASc risk prediction system using data from a prospective multicentre study of patients with imaging confirmed ICH.

8.2 Methods

8.2.1 Clinical data

All data has been taken from the CROMIS-2 ICH study, a prospective multicentre observational study of ICH survivors; full details of the study protocol have been published previously (208). Clinical data used in the prediction models were collected at baseline. Hypertension was defined by a documented history of hypertension or if the patient was taking antihypertensive medication at the time of study entry. Vascular disease was defined as having either ischaemic heart disease or peripheral vascular disease. The end point in this sub-study was the development of ischaemic stroke, death or reaching the final study follow up (defined as 6 months following study enrolment).

We only included patients with ICH and AF who were not started on anticoagulation, because this will alter the future risk of ischaemic stroke. CHA_2DS_2-VASc scores were generated for each patient. ROC curves, Hosmer-Lemeshow tests and corresponding risk estimates comparing subsequent ischaemic stroke events against the CHA_2DS_2-VASc risk estimates(264) were then derived. The observed and predicted risks were then plotted against each other for a visual approximation of fit. We tested the calibration of the CHA_2DS_2-VASc score by fitting a logistic regression model with ischaemic stroke as the outcome and the predicted log-odds of ischaemic stroke (from CHA_2DS_2-VASc) as the only predictor. An intercept and a slope close to 0 and 1 respectively suggested good calibration. Lastly, we used generalized linear models with offset terms to investigate whether we could add additional variables to the CHA_2DS_2-VASc score while keeping the existing variables and their original weightings.

8.2.2 Imaging data

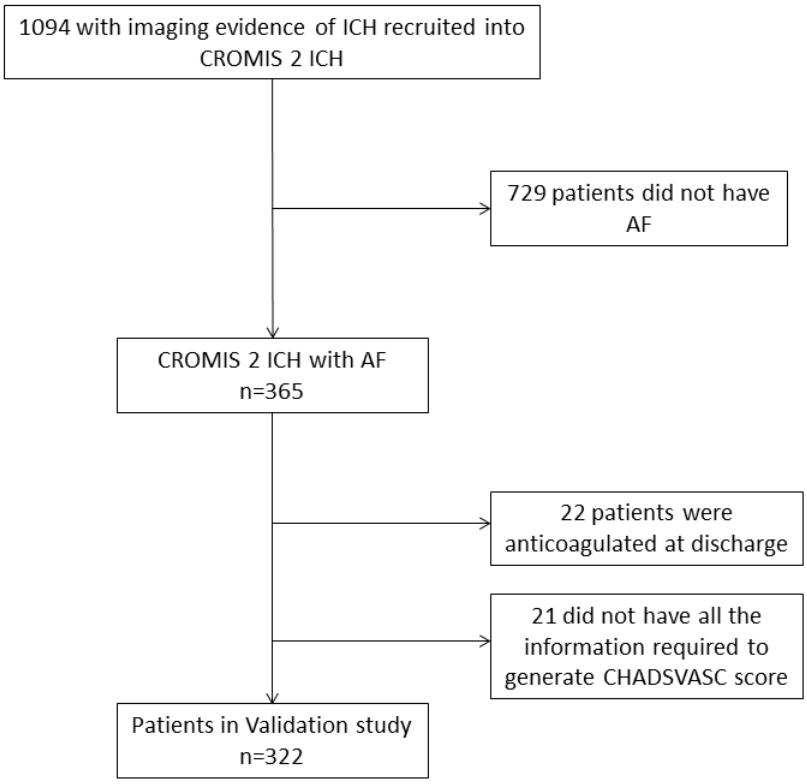
Acute CT scans were rated for leukoaraiosis by a trained research fellow (DW) using a validated scale(249). Leukoaraiosis was then dichotomised into none/mild or moderate/severe based upon whether the score added to a value of ≥3. Lacunar infarction was rated according to STRIVE guidelines(11). A scan was considered “positive” for small vessel disease in the presence of either lacunar infarction or moderate/severe leukoaraiosis. Haematoma location was defined using a published scale (250) and then classified as either

lobar or non-lobar (non-lobar including deep white matter, basal ganglia structures, thalamus, caudate, brainstem and cerebellar).

8.3 Results

Of the 1094 patients in CROMIS-2 ICH, there were 365 patients with concurrent AF. Of these, 22 patients were anticoagulated at discharge and 21 patients lacked the information required to generate a CHA_2DS_2-VASc score; thus, 322 patients were included in the final analysis (Figure 23). There were 17 ischaemic strokes, 7 major bleeding events (all recurrent ICH) and 148 deaths within the follow-up period. Median follow up was 228 days (IQR 186 to 420).

Figure 23 Flowchart of patient entry into the study



Baseline variables are presented in Table 19. When compared with patients included in CROMIS-2 ICH, the CHA_2DS_2-VASc validation cohort was similar, although slightly older and had a higher prevalence of hypertension, hyperlipidaemia, congestive heart failure and previous ischaemic stroke or TIA, they were also less likely to be on antiplatelets at their admission. The median CHA_2DS_2-VASc score was 4 (IQR 3 to 5, range 0 to 7).

Table 19 Baseline characteristics of patients included in validation cohort compared to those not included

Baseline Variable	**CHA_2DS_2-VASc validation cohort(n=322)**	**CROMIS -2 Patients excluded from validation cohort (n=752)**
Age median (SD)	79 (9.2)	71 (13.0)
Sex n (% female)	148 (42)	307 (43)
HTN n (%)	266 (76)	437 (62)
DM n (%)	80 (23)	118 (17)
Hyperlipidaemia n (%)	179 (52)	444 (44)
Congestive heart failure n (%)	33 (10)	16 (2)
Antiplatelets at time of ICH n (%)	59 (17)	212 (30)
Previous ischaemic stroke or TIA n (%)	126 (36)	139 (20)
Previous ICH n (%)	8 (2)	35 (5)
SVD	132 (38)	341 (33)
Lobar location of ICH n (%)	181 (51)	316 (44)

For the observed vs. predicted plots, we dropped CHA_2DS_2-VASc scores where there were less than 10 patients in each category (scores 0, 7 and 8). When compared with the original CHA_2DS_2-VASc development cohort(260) our cohort is older (mean age 78 years vs. 66 years), has a higher prevalence of hypertension (76% vs. 67%), had a greater prevalence of previous ischaemic stroke or TIA (36% vs.9%), whilst having a lower prevalence of congestive heart failure (10% vs. 24%) and vascular disease (27% vs.38%). Comparing the risk predictions adapted from Lip et al(260) (Table 20; Figure 24), our findings showed excellent agreement (Hosmer-Lemeshow goodness of fit p=0.85; no evidence of lack of fit). The calibration was also satisfactory (slope 1.02 and intercept 0.21, p=0.80), with no evidence of a difference. The C statistic was 0.64.

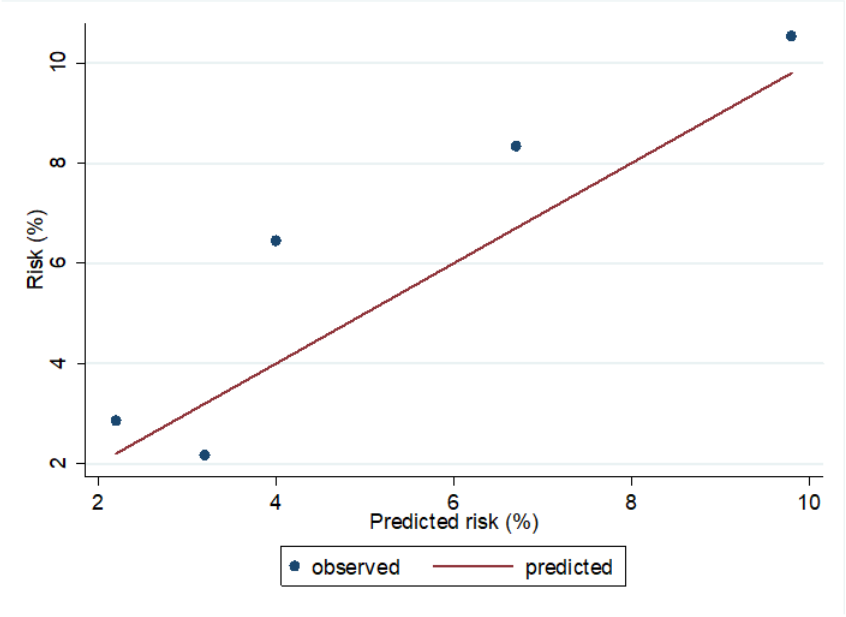
Neither the addition of ICH location (OR 2.01, 95% CI 0.72 to 5.61, p=0.181) nor SVD presence (OR 0.82, 95% CI 0.29 to 2.29, p=0.703) to the existing CHA_2DS_2-VASc improved the predictive power for ischaemic stroke in this population.

Table 20 Actual observations vs. predicted observations in ICH cohort with AF

CHA_2DS_2-VASc score	Actual risk of stroke % (n/N) [95% CI]	Predicted risk of stroke %
2	2.9 (1/35) [0.1 to 14.9]	2.2
3	2.2 (2/92) [0.2 to 7.6]	3.2
4	6.5 (6/93) [2.4 to 13.5]	3.8
5	8.3 (6/72) [3.1 to 17.3]	6.7
6	10.5 (2/19) [1.3 to 33.1]	9.8

Key. Predicted observations adapted from Lip et al 2010, available at chadsvasc.org

Figure 24 Observed vs Predicted plot of ICH recurrence



Footnote: Predicted observations adapted from Lip et al 2010, available at chadsvasc.org

8.4 Discussion

We have validated the CHA_2DS_2-VASc scoring system in a population of ICH survivors with AF by showing firstly that on average the predicted risks are similar to the observed risks, and secondly that the score has a similar predictive value (as judged by the C-statistic) in an ICH population as has been reported in other AF populations. Interestingly, we found that the risk of ischaemic stroke is higher in ICH patients with AF than that of a population-based AF cohort

To the best of our knowledge, this is the first study to validate the CHA_2DS_2-VASc score in an ICH population. Whilst we observed slightly higher ischaemic stroke risks by CHA_2DS_2-VASc score than those reported in a population-based cohort, the increase in risk with each point increase in CHA_2DS_2-VASc was similar. Although our C-statistic showed moderate discrimination (0.64), this is comparable with other validation cohorts for CHA_2DS_2-VASc including ischaemic stroke populations(264). The higher event rate of ischaemic stroke in our population may be explained by an increased risk of lacunar infarction due to the expected high prevalence of cerebral small vessel disease. Unlike population-based AF cohorts, patients with primary ICH are likely to have underlying small vessel disease and therefore are at higher risk of lacunar infarction. Indeed, of the 17 ischaemic strokes, only 11 were cardioembolic, three were small vessel occlusion and three were unknown. Furthermore, our patient group was also older and had a higher prevalence of hypertension and previous ischaemic stroke or TIA.

Our study has strengths. CROMIS-2 is a large prospectively recruited multicentre study of ICH survivors which should be representative of a Western ICH survivor population, and we were able to include many ICH patients with AF. Although there were some differences in demographics and risk factor profiles between our validation cohort and the total study population, the differences are expected given AF is associated with age and vascular risk factors (269). Furthermore, very few of our patients with ICH and AF were restarted on anticoagulation, suggesting there is little selection bias. Despite these strengths, our study does have some limitations. We do not have information on anticoagulation after discharge, which might affect the risk of ischaemic stroke. We used CT rather than MRI measures of small vessel disease as only a subset of patients had MRI imaging; MRI would have

allowed more detailed analysis of the structural neuroimaging markers of small vessel disease (for example, quantification of cerebral microbleeds and MRI-visible perivascular spaces). We could not explore major bleeding risk scores (i.e. HAS-BLED) within our cohort as we only had 7 recurrent ICH events, and our cohort included only patients not known to be taking anticoagulation after ICH.

PART 4

DISCUSSION, CONCLUSIONS AND FUTURE DIRECTIONS

9.0 Discussion and Conclusions

Our understanding of ICH has progressed immensely over the past decade. We have moved away from the label ‘primary’ ICH reflecting our greater understanding of the mechanism underlying most cases of spontaneous ICH: cerebral small vessel disease (11). Epidemiological studies of ICH have identified key risk factors of which hypertension along with alcohol intake and psychosocial factors are the most important (270, 271). Clinical risk scores have been developed to help clinicians with difficult anticoagulant decisions (213, 272, 273), albeit with modest ability to predict ICH (274). The increasing role of neuroimaging in patients with CAA help push our understanding of this devastating condition further: pathological validation studies using neuroimaging biomarkers to diagnose CAA have been published (111, 275), including a CT based diagnostic criteria (276). In addition to CMBs and cSS, high grade centrum semiovale perivascular spaces (107, 174, 277, 278), cortical atrophy (279), blood-oxygen level-dependent (BOLD) response on functional MRI (280-282) and amyloid PET (using various ligands) (282-284) have all shown promise as useful biomarkers in identifying patients with CAA. Despite these advancements, the incident of ICH has remained stable, or even increasing in some populations (4, 7), what’s more, some of these advancements have led to clinical uncertainty; for example, the clinical implications of CMBs, or cortical superficial siderosis in patients without intracerebral haemorrhage, especially regarding antithrombotic treatment.

In chapter one and two, I outline our current understanding of the mechanisms underlying spontaneous intracerebral haemorrhage: namely, small vessel disease. I review selected neuroimaging markers of small vessel disease and their relationship to intracerebral haemorrhage. In the third chapter, I identify current gaps in our knowledge, which the work in my thesis aimed to fill.

In this chapter, I briefly summarise the main findings described in chapters 4-8 and, together with the other available published literature, attempt to fill the gaps in knowledge identified in chapter three. Finally, in chapter 10, I highlight some remaining gaps in knowledge relevant to ICH and suggest directions for future research.

9.1 Summary of our main findings

ICH and ischaemic stroke risk associated with CMBs in patients with ischaemic stroke

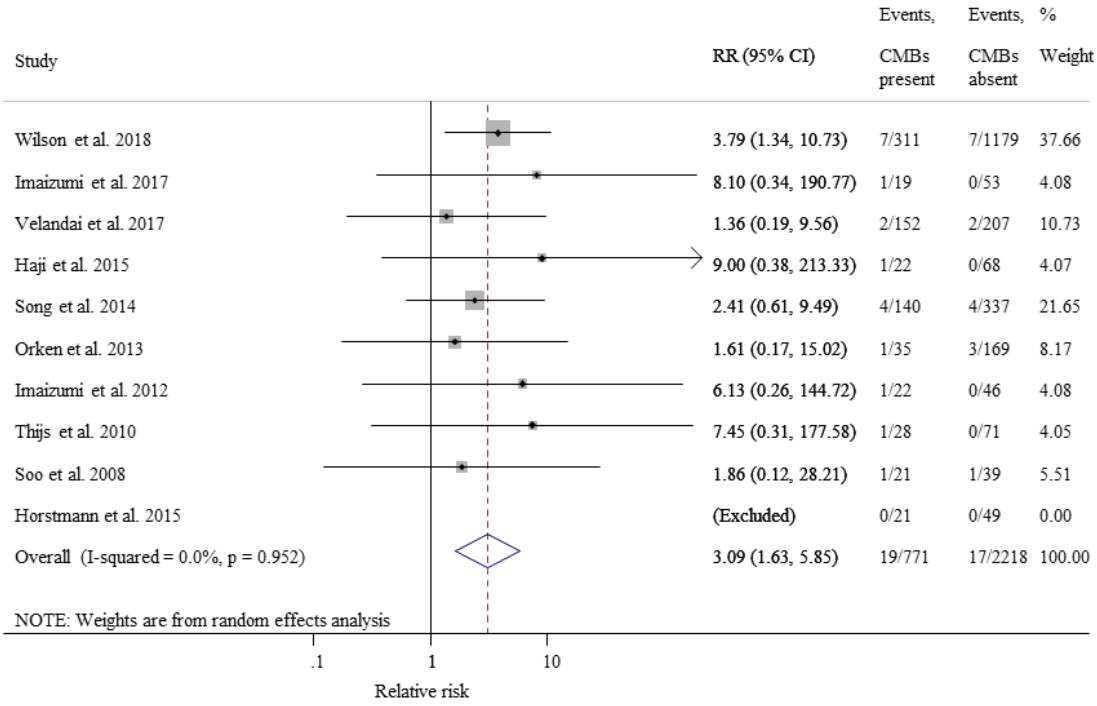
The identification of CMBs as a marker of a 'bleeding prone arteriopathy' was originally based on their strong association with ICH populations (124, 125). Few data existed from ischaemic stroke populations, though small single centre studies in mainly Western populations suggested that CMBs are also associated with ischaemic stroke recurrence (189-192, 195).

In chapter four I describe an aggregate-level meta-analysis including published and unpublished data to obtain more accurate estimates of the rate and risks of ICH and IS in patients with ischæmic stroke who have CMBs. We stratified CMB by burden and distribution and explore how these interact with ICH and ischaemic stroke risk. We showed that CMBs are associated with both ICH and ischaemic stroke, but that a clear dose relationship only exists for ICH risk. Indeed, patients with five or more CMBs (compared to those with none), have a 4 times higher risk for ICH than ischaemic stroke. However, the absolute rates of ischaemic stroke were higher than the rates of ICH in all categories of CMB burden. Regarding CMB distribution; those with strictly lobar and mixed CMBs had the highest risk of ICH (compared to those with none) however, we could not account for differences in CMB burden within these patients. A recent observational study including two large western and eastern populations investigated the time course of risks of ischaemic stroke and haemorrhage events in people exposed to antiplatelets after ischaemic stroke or TIA (285). They show IS risk is substantially higher than ICH risk within the first one year, even in patients with a high burden (≥5) of CMBs, but after this time the risk of ICH matches that of IS. Taken together these studies provides clinicians with some reassurance regarding prescribing antiplatelet medications in stroke, even in patients with high CMBs burdens. However, as antiplatelets are most effective very early after stroke or TIA with a diminishing benefit over long-term use (286), whether antiplatelets provide a net benefit in patients with high CMB burdens after the first one year post-TIA or stroke is unknown. In the absence of randomized controlled trials, patients with high CMB burden should continue to be treated by best medical practice but perhaps counselled regarding higher risks of ICH with a more aggressive management of modifiable risk factors such as alcohol

intake and hypertension. Our results are not generalizable to patients taking oral anticoagulants, however, as most patients in our meta-analysis were taking antiplatelet drugs.

In chapter five we review the association of CMBs with ICH and ischaemic stroke risk in patients with ischaemic stroke secondary to AF. CROMIS-2 is the first study adequately powered to evaluate whether CMBs are associated with an increased risk of ICH in patients with ischaemic stroke who require anticoagulation. We provide new evidence in patients with ischaemic stroke or TIA and atrial fibrillation, that CMB presence is an independent risk factor for intracranial haemorrhage (adjusted HR 3·67 (95% CI 1·27 to 10·60)). Combining our data with previously published studies confirms our findings and provides a more precise estimate of the association of CMBs with intracranial (or intracerebral) haemorrhage (Figure 25). We also show the risk of intracranial haemorrhage increases as CMB burden increases, but that the absolute event rate for ischaemic stroke remains higher than that for intracranial haemorrhage, even in patients with multiple CMBs. We developed and internally validated a simple risk prediction model for intracranial haemorrhage, showing for the first time that the inclusion of CMB presence as a neuroimaging biomarker improves the predictive value of a commonly used bleeding risk score based on clinical data alone (HASBLED). Our study firmly establishes that CMBs are an independent risk factor for subsequent intracranial haemorrhage in a Western population of patients with ischaemic stroke or TIA associated with AF and treated with anticoagulants. Furthermore, our study provides proof of concept that the addition of a neuroimaging biomarker (CMBs) improves the predictive ability of clinical risk scores for intracranial haemorrhage, a deadly complication of oral anticoagulation. This could help clinicians and patients make better-informed anticoagulation decisions. Our findings support further pooled individual participant data meta-analyses of data from large prospective cohorts to increase the precision of our risk estimates and determine whether high CMB counts might be associated with a sufficiently high risk of intracranial haemorrhage to identify patients who will suffer net harm from oral anticoagulation. Additionally, pooled data should be used to refine and validate an intracranial haemorrhage risk score incorporating clinical factors and CMBs.

Figure 25 Forest plot of all prospective studies in patients on anticoagulation evaluating ICH relative risk with compared to without CMBs



Additional value of small vessel disease markers in identifying a macrovascular cause for ICH

In chapter six we show markers of small vessel disease are a clinically useful predictor for identifying the absence of an underlying macrovascular cause for an ICH. Indeed, combining the presence/absence of small vessel disease markers with the results of a CT angiogram and history of whether the patient has hypertension, allows better risk categorization to help identify patients who should undergo invasive imaging to search for an underlying macrovascular cause. Due to selection bias, our results are only generalizable to a young population of patients with ICH, but this is likely to be the group in whom macrovascular causes are most common. Our score needs to be externally validated before clinical use. A similar score based on a prospective study was undertaken in the Netherlands (287). Our patient population served as the validation cohort for their model. After validation, their model incorporating CTA findings, CT SVD markers, age and ICH location achieved a C statistic of 0.88 (95% CI 0.83 to 0.94) for predicting an underlying macrovascular lesion as the cause for ICH. The model is displayed in figure 26 and shows the added value of identifying SVD in this patient population.

Figure 26 Prediction charts with absolute probabilities (%) of an underlying macrovascular cause in individual patients with ICH. CTA, CT angiography

Patient characteristics, NCCT and CTA (DIAGRAM+ score)							
CTA Negative							
Age 18-50 years				Age 51-70 years			
	Deep	Lobar	Posterior Fossa		Deep	Lobar	Posterior Fossa
SVD	1	5	.	SVD	1	2	4
No SVD	9	29	51	No SVD	3	11	24
CTA Positive							
Age 18-50 years				Age 51-70 years			
	Deep	Lobar	Posterior Fossa		Deep	Lobar	Posterior Fossa
SVD	14	.	.	SVD	.	17	34
No SVD	56	84	93	No SVD	28	61	79

Low	1-5%
Intermediate	6-25%
High	>25%

From Hilkens et al: J Neurol Neurosurg Psychiatry. Jan 18. pii: jnnp-2017-317262

Risk of recurrent ICH and new ischaemic stroke after ICH.

Restarting antithrombotics in patients with an indication for antithrombotics after they suffer from ICH is a longstanding clinical conundrum (128, 288, 289). Clinical practice varies widely by country (290) and up until recently expert opinion was to avoid restarting anticoagulation in patients with ICH, especially if their ICH was in the lobar regions (128, 288, 289). In the past three years there have been many observational studies investigating anticoagulant resumption after ICH: a meta-analysis of 8 such studies shows resumption of anticoagulation was associated with a lower risk of thromboembolic complications (pooled relative risk, 0.34; 95% confidence interval, 0.25-0.45) without an increased risk of recurrent ICH (pooled relative risk, 1.01; 95% confidence interval, 0.58-1.77) (291), unfortunately ICH location was not considered. A meta-analysis of three studies (n=1012) which included ICH location as a variable, showed that even in lobar ICH (n=379) (292), resumption of OACs is associated with decreased mortality (HR 0.29, 95% CI 0.17-0.45) and improved functional outcome (HR 4.08, 95% CI 2.48-6.72). In chapter seven I show that ICH location is an important determinant in that lobar ICH location is associated with recurrent ICH but inversely associated with new ischaemic stroke (albeit not reaching conventional statistical significance). Whilst history of a previous ischaemic stroke or atrial fibrillation were independent risk factors for new IS. Unfortunately, we did not collect information on antithrombotic medication at follow up so could not investigate the interaction between antithrombotic (re)start and ICH location. Nonetheless, our study further validates the importance that ICH location should be considered when considering recurrent event risk. We await randomised control trials (RESTART (ISRCTN71907627), SoSTART (NCT03153150), RESTART-FR (NCT02966119), STATICH (NCT03186729), NASPAF-ICH (NCT02998905), A3-ICH (NCT03243175), ASPIRE, APACHE-AF (NCT02565693)) to conclusively answer this clinical conundrum.

In chapter eight I explore whether the widely used ischaemic stroke risk prediction score CHA_2DS_2VASC can be used in patients with ICH. Validating such a risk score can help clinicians weigh up antithrombotic decisions in patients with ICH, whilst we await conclusive guidance from the results of ongoing RCTs. We show the CHA_2DS_2VASC score has similar risk predictions for subsequent IS in an ICH cohort to the risk derived from an AF cohort largely without ICH. There was no statistical improvement in prediction

for CHA_2DS_2VASC with the addition of CT positive markers of small vessel disease, nor ICH location.

These two studies, taken together with the available literature, can help clinicians risk stratify patients who suffer ICH and have an ongoing indication for anticoagulants. Observational data suggest resumption of anticoagulants seems to lead to a net benefit and may be preferred, especially in those patients with high CHA_2DS_2VASC scores. Patients with lobar ICH should be monitored closely with aggressive treatment of their modifiable risk factors for recurrent ICH. Until the results of RCTs of antithrombotic therapy after ICH (RESTART, SoSTART, RESTART-FR, STATICH-antiplatelets/anticoagulants, NASPAF-ICH, A3-ICH, ASPIRE, APACHE-AF) become available, conclusive answers to this important clinical question remain unanswered.

10. Future directions

10.1 Markers of small vessel disease in ischaemic stroke populations: Individual patient data meta-analysis

The rarity of ICH in ischaemic stroke populations coupled with the need for long-term follow up make RCTs a challenging method to further explore how markers of small vessel disease relate to future ICH risk associated with different antithrombotic treatment strategies in high-risk populations. Nevertheless, a recent trial of 1534 patients with non-cardioembolic stroke or TIA who were thought to be at high risk of ICH (history of or neuroimaging findings of intracerebral haemorrhage or two or more microbleeds) shows in these patients, cilostazol was non-inferior to aspirin in preventing a composite of vascular events and non-superior in preventing adverse (bleeding) events (293). They did not explore whether these risks change with increasing CMB burden. In the absence of very large randomised controlled trials, larger scale observational individual patient meta-analyses should help to answer this question. Only through large numbers can we have access to sufficient ICH and IS events to validate scoring systems and to explore whether there is a burden of CMBs that might tip the balance away from antithrombotic treatment to avoid net harm. Our team is currently leading on one such effort with over 35 centres and 18000 individual patients, including over 7000 on anticoagulation contributing data (294).

Alternative treatment options would include: avoidance of antithrombotics, short-term rather than long-term use of antithrombotics (in the case of antiplatelet therapy for non-cardioembolic stroke), use of antithrombotics which are less likely to cause ICH (e.g. NOACs rather than VKA), left atrial appendage occlusion (295) (in patients with AF) or continuation of antithrombotics with closer follow up and aggressive management of modifiable risk factors (e.g. hypertension).

It is important to recognize that the use of observational data, even from large-scale collaborations does have important potential limitations:

- All patients have had an ischaemic stroke and therefore have an ongoing indication for antithrombotics (either antiplatelets or anticoagulation). The absolute incidence of ICH would, therefore, have to far outweigh the absolute incidence of IS if we are

to find a burden of CMBs where the balance tips away from antithrombotics.

- The observational nature of the data means any recommendations relating to antithrombotic decisions will not be founded on the highest level of evidence.
- Variables in potential risk scores for ICH and IS are likely to have considerable overlap: HASBLED and CHA_2DS_2VASC share 3 variables, and in chapter 3 we show CMBs are both a risk factor of ICH and IS, which makes finding a risk score which discriminately targets ICH challenging.

10.2 Identification of ICH specific biomarkers

SVD underlies most cases of spontaneous ICH (77-88% (296)) and many cases of IS (up to 50% (297)). Identifying which patients with SVD will go on to have haemorrhagic complications and which patients go on to have ischaemic complications remains a key research and clinical goal. Biomarkers of SVD (both imaging and non-imaging) may provide a framework for this. Indeed, cSS and APOE ε4 have shown some promise (275).

A biomarker (biological marker) can be defined in numerous ways. The national institute of health defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (298). The World Health Organisation has an even broader definition "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease" (see http://www.inchem.org/documents/ehc/ehc/ehc222.htm).

An ideal biomarker should be involved in the causal pathway of the disease in question. Ideally fulfilling the 'trait, state and rate criteria', where trait indicates the patient is likely to develop the disease if the biomarker is present, state indicates the biomarker itself can be part of a diagnostic criteria for the disease, and rate suggests the biomarker can be used to monitor the rate of disease progression.

The difficulty in stroke medicine is many of the biomarkers which fulfill the trait, state and rate criteria for ICH, perform equally well for ischaemic stroke, for example, CMBs and WMHs, so their presence cannot inform antithrombotic decisions. A fourth biomarker criterion is desirable: 'discrimination', where the biomarker is unique to one aspect of a

heterogeneous disease (in the case of stroke medicine, a key aim is to discriminate between future ischaemic stroke and ICH risks).

One potentially interesting biomarker of small vessel disease fulfilling all four of these criteria is cSS. Patients with cSS have a high risk of subsequent ICH (145), its presence is used in the modified Boston criteria of CAA (137) and there is a clear dose-dependent relationship between the degree of cSS and likelihood of developing an ICH (147). Moreover, cSS seems to be unique to CAA and does not increase the risk of IS. Unfortunately, it is likely that the low prevalence and specificity in patients at risk of ICH are too low for cSS to have widespread clinical application. GDF-15, a biomarker associated with cellular ageing, cellular growth, oxidative stress and inflammation has been shown to predict major bleeding in patients with AF, so is also promising (299). Unfortunately, this same biomarker was not tested in its predictive capabilities for IS. This is an opportunity for further research.

The relative rarity of ICH when compared with IS, coupled with the fact they both share many risk factors ultimately means that one single biomarker is unlikely to be sufficient to guide antithrombotic treatments. Instead, a risk score could be developed incorporating many biomarkers: clinical (for example age and a history of hypertension and previous ICH), neuroimaging (for example CMBs and cSS), circulating biomarkers (such as GDF-15) and genetic biomarkers (such as APOE). If validated in large observational registries one could envisage a randomized control trial where the risk scores for ICH and ischaemic stroke could be used to guide antithrombotic decisions and compared with usual care to see if their use improves patient outcomes and quality of life.

10.3 CAA pathological-radiological validation studies in non-ICH cohorts

Much of the pathological validation studies undertaken in validating MRI markers of small vessel disease have been in ICH and memory clinic cohorts. The use of the Boston criteria to diagnose CAA in patients without ICH or cognitive decline is unfounded and potentially misleading. Indeed, a pathological validation study in patients without ICH shows the Boston criteria has a positive predictive value of only 25% in diagnosing CAA in healthy community patients (111). Furthermore, the sensitivity of the Boston criteria was only 4.5%

in this cohort. Another cohort without ICH, but in a hospital for various reasons had a higher positive predictive value for diagnosing CAA (87.5%). These two cohorts differed dramatically in CMB burden, the former having a median CMB count of 2 (range 1-7), the latter a median lobar MB count of 20 (range 1-129). The authors suggest, in patients without ICH, the Boston criteria should only be applied to patients with symptoms attributable to CAA. I suggest it is CMB burden rather than clinical context which is important. Great caution should be undertaken when using the Boston criteria in patients without ICH who have low CMB burden, regardless of clinical context (112).

Vascular brain banks should be established and further histopathological-radiology validation patients without ICH undertaken. Neuroimaging biomarkers which show some promise with diagnosing CAA in ICH patients (centrum semiovale PVS, cortical atrophy, BOLD response on functional MRI and amyloid PET ligands) should also be investigated in patients without ICH. Until such time, researchers should not attribute certain MRI patterns of SVD to a small vessel disease subtype in patients without ICH. The risk associated with these MRI markers should remain just that, and not be considered the risk associated with a putative diagnosis of CAA. Lastly, in ICH and non-ICH cohorts, CMB distribution should be revisited. It seems unlikely a patient with multiple lobar CMBs and one deep CMB would not have CAA, a lobar/deep ratio should be validated using histopathologically confirmed CAA and non-CAA patients.

10.4 Identifying predictors of a macrovascular cause in ICH patients

The prevalence of macrovascular causes of ICH may still be underestimated: There are only two studies which are free from selection bias in which IADSA was undertaken in patients with ICH: One small single centre study (n=102) in which all patients with ICH who were well enough to undergo IADSA were enrolled (16) and another small single centre study (n=206) where consecutive patients with ICH underwent IADSA (15). The former study reported rates of structural lesions underlying basal ganglia and cerebellar ICHs in 31% and 18% of patients respectively. Furthermore, a structural lesion accounted for 11% of ICH in older hypertensive patients; the authors concluded IADSA should be undertaken if the patient is well enough rather than being driven by variables such as age, hypertension and ICH location. These findings have been overshadowed by the latter study,

where the authors reported 0/29 (0%) of patients older than 45, with hypertension and an ICH location in the basal ganglia, thalamic region or posterior fossa had an underlying macrovascular cause. This finding is often quoted in subsequent studies as a reason for excluding patients with these characteristics from undergoing IADSA. Indeed, in our own cohort, we found three macrovascular causes in patients over 45 years old, with deep ICH location and a history of hypertension.

I suggest prospective studies which include consecutive patients with ICH who are well enough to undergo MRI be undertaken. All patients should have CT and CTA, followed by acute (within 7 days) MRI with paramagnetic sequences (allowing for more sensitive analysis of small vessel disease (CMBs, cSS) and arterial spin labeling (ASL). A small study in Japan shows ASL can detect pooled blood in diseased veins in patients with dural fistulas and successfully identified 12/13 patients with ICH who had a dural fistula (300). Patients with suspicious lesions on any of these modalities should undergo acute IADSA. In those who do not have suspicious lesions, a delayed MRI and ASL should be undertaken three months following the ICH

10.5 Cryptogenic ICH

Patients who have an ICH where, despite intensive investigation (CTA, IADSA, MRI), we are unable to find a cause are termed to have ‘cryptogenic ICH’. The likely differential for these patients is either: a) an acute focal region of small vessel disease too small to visualize on MRI, or b) a macrovascular lesion which was obliterated in the ICH. This patient group needs more attention. We do not know the natural history of these patients and require more detail regarding their underlying histopathology. Patient registries should be established to examine the rate of ICH recurrence in these patients and whether it differs from patients with a known cause for their ICH. Where possible, tissue should be taken, either pre-mortem or post-mortem looking for any signs of a macrovascular lesion or small vessel disease not detected on neuroimaging. The more widespread use of ASL in patients without ICH may also lead to the detection of incidental AV shunts, the natural history of which (if patients do not undergo treatment) may also help resolve whether obliterated macrovascular lesions are responsible for many cryptogenic ICH cases.

10.6 Automated neuroimaging ratings

Manual detection of the various markers of small vessel disease is time consuming and arduous. Future studies in ICH will require large-scale collaborations where manual rating is likely to be a rate-limiting step. Identification and quantification of neuroimaging markers of small vessel disease need to become fully automated to allow rapid identification and quantification and reduce inter-rater variability.

Of the current neuroimaging markers of small vessel disease, automated white matter hyperintensities lesion mapping and volume assessment are the most advanced. Many different algorithms have been developed, mostly in MRI(301) (302) but more recently in CT (303). Indeed, the CT based algorithm correlated with gold standard MRI volumes reliably with higher burdens of white matter disease (Fazekas 2 and 3) but performed poorly with mild burdens of white matter disease. Automated detection of cerebral microbleeds has also been pursued. These algorithms consistently show excellent reliability (303, 304) both at baseline and in longitudinal measures. One consistent problem with automated CMB ratings are the high rates of false negative CMBs when compared to a 'gold standard' human rater. The false detection rates can be as high as 27 CMBs per subject (304). Despite this false detection rate, the use of one algorithm with very little variability over large multicentre datasets remains an attractive proposal. Whilst previous risks attributed to CMBs clearly cannot be applied in these situations, the same is probably true for manual CMB rating as improving MRI technology with stronger magnet strengths can now identify a greater number of CMBs when compared with T2* GRE in which the risk scores were originally modelled upon. Automated lesion mapping and volume of ICH also needs to be undertaken. Manual or semi-automated lesion and ICH volume rating are cumbersome and time-consuming, furthermore, there is marked variability in the semi-automated approach depending on the software (305). One such method has been published (306) and we currently plan to undertake similar analyses using data from CROMIS-2 ICH.

10.8 Imaging with 7 Tesla MRI and 'vascular reserve'

In addition to the improved imaging of the consequences of small vessel disease, recent advancements with high resolution 7 Tesla MRIs now allow for assessment of the smaller vessels themselves and their vessel walls. Furthermore, BOLD imaging on MRI and CO_2

challenges on transcranial doppler allow us to explore ‘vascular reserve’ in blood vessels - the blood vessels adaptive ability to respond to changes in blood flow. These advancements offer further opportunity to understand the pathogenesis of SVD and how it may relate to ICH.

Studies in 7 Tesla MRI show improved resolution and sensitivity for neuroimaging biomarkers of SVD: Perivascular spaces are seen in greater detail and the internal structure of lacunes are better visualized (307). CMBs and CMIs are also seen in greater numbers on 7 Tesla vs. 1.5 Tesla (308) or 3 Tesla (309). Vessel wall imaging at 7 Tesla can visualize basal intracranial wall disease and can visualize single perforators off associated with lacunar infarction(310). Such work may give insights into which imaging characteristics give rise to occlusion and which give rise to ICH. Finally, studies in vascular reserve and vascular reactivity also offer promise in SVD: BOLD response to visual stimulus is decreased in patients with CAA (280) and continues to decrease over time, independent of CMB and WMH burden (282) highlighting studies in vascular reserve are important in monitoring disease progression.

10.9 Main conclusions

Neuroimaging biomarkers of small vessel disease provide a framework to help diagnose and stratify risk in patients at risk of ICH. The use of these neuroimaging biomarkers is likely to be a key step toward 'personalized and precision medicine'.

'Personalised medicine'(311) is an important departure from the 'one size fits all' approach previously used in stroke medicine. Using biomarkers and genetic data we hope to better tailor treatments to the individual rather than the diagnosis of 'stroke'. Through personalised medicine, we also hope to identify people at risk of diseases before they have symptoms, with the aim of preventing them all together through personalised treatments. Precision medicine is a similar concept where treatments are tailored to individual patient characteristics with investigations targeted towards those who will most benefit.

In stroke medicine, the concepts of 'personalized medicine' and 'precision medicine' can have particular value. Stroke is simply a syndrome where the same clinical presentation (usually a sudden-onset focal neurological syndrome) can be caused by ischaemic stroke or ICH, each with a range of vastly differing aetiologies. Furthermore, the underlying cause of the majority of ICH and a substantial proportion of IS, is the same pathological process: SVD. Identifying which patients with SVD will go on to have ICH and which patients will have IS remains a key research aim.

The data I have presented provide evidence that CMBs might be a promising neuroimaging biomarker in ischaemic stroke to facilitate personalised medicine. The addition of CMBs to clinical risk scores improves the predictive power to identify patients at risk of ICH with potential relevance for clinical practice and trials. However, it remains unclear whether there is a burden of CMBs which may tip the balance away from antithrombotic medication because of the risk of net harm. Large international collaborations may help identify burdens and distributions of CMBs, which, along with other neuroimaging biomarkers (cSS for example), vascular risk factors, and genetic data may allow us to tailor treatments.

Identifying small vessel disease in patients with ICH helps tailor further investigation. We show together with CTA findings and a clinical history of pre- ICH hypertension,

identification of SVD can accurately risk-stratify patients into likelihoods of having an underlying macrovascular cause: patients with SVD, a ‘negative CTA’ and a history of hypertension should not undergo invasive IASDSA, an idea that reflects a key concept of precision medicine.

Lastly, we show the location of ICH is positively associated with recurrent ICH risk and negatively associated with new ischaemic stroke risk (albeit the latter not statistically significant), although CT based identification of small vessel disease did not seem to provide any predictive power for either recurrent ICH or new ischaemic stroke. Whilst we await the results of trials for restarting antithrombotics in patients with ICH, clinicians should be mindful of ICH location. Further studies of individual SVD component markers on CT or MRI are needed to assess their prognostic value. Meanwhile, CHA_2DS_2VASC is a reasonable predictor of ischaemic stroke risk in this patient population and can be used to help weigh up potentially difficult anticoagulant decisions.

References

1. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project--1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral and subarachnoid haemorrhage. Journal of neurology, neurosurgery, and psychiatry. 1990;53(1):16-22.
2. Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International Stroke Incidence Collaboration. Stroke; a journal of cerebral circulation. 1997;28(3):491-9.
3. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. Journal of neurology, neurosurgery, and psychiatry. 2013.
4. van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet neurology. 2010;9(2):167-76.
5. Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet neurology. 2009;8(4):355-69.
6. Carandang R, Seshadri S, Beiser A, Kelly-Hayes M, Kase CS, Kannel WB, et al. Trends in incidence, lifetime risk, severity, and 30-day mortality of stroke over the past 50 years. JAMA : the journal of the American Medical Association. 2006;296(24):2939-46.
7. Bejot Y, Cordonnier C, Durier J, Aboa-Eboule C, Rouaud O, Giroud M. Intracerebral haemorrhage profiles are changing: results from the Dijon population-based study. Brain : a journal of neurology. 2013;136(Pt 2):658-64.
8. Lovelock CE, Molyneux AJ, Rothwell PM, Oxford Vascular S. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. Lancet neurology. 2007;6(6):487-93.
9. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology. 2007;68(2):116-21.
10. Wilson D, Adams ME, Robertson F, Murphy M, Werring DJ. Investigating intracerebral haemorrhage. Bmj. 2015;350:h2484.
11. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. The Lancet Neurology. 2013;12(8):822-38.
12. Dawkins AA, Evans AL, Wattam J, Romanowski CA, Connolly DJ, Hodgson TJ, et al. Complications of cerebral angiography: a prospective analysis of 2,924 consecutive procedures. Neuroradiology. 2007;49(9):753-9.
13. Cordonnier C, Klijn CJ, van Beijnum J, Al-Shahi Salman R. Radiological investigation of spontaneous intracerebral hemorrhage: systematic review and trinational survey. Stroke; a journal of cerebral circulation. 2010;41(4):685-90.
14. Toffol GJ, Biller J, Adams HP, Jr., Smoker WR. The predicted value of arteriography in nontraumatic intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 1986;17(5):881-3.

15. Zhu XL, Chan MS, Poon WS. Spontaneous intracranial hemorrhage: which patients need diagnostic cerebral angiography? A prospective study of 206 cases and review of the literature. Stroke; a journal of cerebral circulation. 1997;28(7):1406-9.
16. Halpin SF, Britton JA, Byrne JV, Clifton A, Hart G, Moore A. Prospective evaluation of cerebral angiography and computed tomography in cerebral haematoma. Journal of neurology, neurosurgery, and psychiatry. 1994;57(10):1180-6.
17. Hill AB. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine. 1965;58:295-300.
18. Neuropathology Group. Medical Research Council Cognitive F, Aging S. Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet. 2001;357(9251):169-75.
19. Devan WJ, Falcone GJ, Anderson CD, Jagiella JM, Schmidt H, Hansen BM, et al. Heritability estimates identify a substantial genetic contribution to risk and outcome of intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2013;44(6):1578-83.
20. Fischer U, Cooney MT, Bull LM, Silver LE, Chalmers J, Anderson CS, et al. Acute post-stroke blood pressure relative to premorbid levels in intracerebral haemorrhage versus major ischaemic stroke: a population-based study. Lancet neurology. 2014;13(4):374-84.
21. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955-62.
22. Arboix A, Vall-Llosera A, Garcia-Eroles L, Massons J, Oliveres M, Targa C. Clinical features and functional outcome of intracerebral hemorrhage in patients aged 85 and older. Journal of the American Geriatrics Society. 2002;50(3):449-54.
23. D'Amore C, Paciaroni M, Silvestrelli G, Agnelli G, Santucci P, Lanari A, et al. Severity of acute intracerebral haemorrhage, elderly age and atrial fibrillation: independent predictors of poor outcome at three months. European journal of internal medicine. 2013;24(4):310-3.
24. Provencio JJ, Da Silva IR, Manno EM. Intracerebral hemorrhage: new challenges and steps forward. Neurosurgery clinics of North America. 2013;24(3):349-59.
25. Dequatre-Ponchelle N, Henon H, Pasquini M, Rutgers MP, Bordet R, Leys D, et al. Vitamin K antagonists-associated cerebral hemorrhages: what are their characteristics? Stroke; a journal of cerebral circulation. 2013;44(2):350-5.
26. Flaherty ML, Tao H, Haverbusch M, Sekar P, Kleindorfer D, Kissela B, et al. Warfarin use leads to larger intracerebral hematomas. Neurology. 2008;71(14):1084-9.
27. Ma M, Meretoja A, Churilov L, Sharma GJ, Christensen S, Liu X, et al. Warfarin-associated intracerebral hemorrhage: Volume, anticoagulation intensity and location. Journal of the neurological sciences. 2013;332(1-2):75-9.
28. Falcone GJ, Brouwers HB, Biffi A, Anderson CD, Battey TW, Ayres AM, et al. Warfarin and Statins are Associated with Hematoma Volume in Primary Infratentorial Intracerebral Hemorrhage. Neurocritical care. 2013.
29. Cucchiara B, Messe S, Sansing L, Kasner S, Lyden P, Investigators C. Hematoma growth in oral anticoagulant related intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2008;39(11):2993-6.
30. Flibotte JJ, Hagan N, O'Donnell J, Greenberg SM, Rosand J. Warfarin, hematoma expansion, and outcome of intracerebral hemorrhage. Neurology. 2004;63(6):1059-64.
31. Brouwers HB, Chang Y, Falcone GJ, Cai X, Ayres AM, Battey TW, et al. Predicting Hematoma Expansion After Primary Intracerebral Hemorrhage. JAMA neurology. 2013.

32. Horstmann S, Rizos T, Lauseker M, Mohlenbruch M, Jenetzky E, Hacke W, et al. Intracerebral hemorrhage during anticoagulation with vitamin K antagonists: a consecutive observational study. Journal of neurology. 2013;260(8):2046-51.
33. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet neurology. 2010;9(7):689-701.
34. Greenberg SM, Vonsattel JP. Diagnosis of cerebral amyloid angiopathy. Sensitivity and specificity of cortical biopsy. Stroke; a journal of cerebral circulation. 1997;28(7):1418-22.
35. Tanskanen M, Makela M, Myllykangas L, Notkola IL, Polvikoski T, Sulkava R, et al. Prevalence and severity of cerebral amyloid angiopathy: a population-based study on very elderly Finns (Vantaa 85+). Neuropathology and applied neurobiology. 2012;38(4):329-36.
36. Fryer JD, Simmons K, Parsadanian M, Bales KR, Paul SM, Sullivan PM, et al. Human apolipoprotein E4 alters the amyloid-beta 40:42 ratio and promotes the formation of cerebral amyloid angiopathy in an amyloid precursor protein transgenic model. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2005;25(11):2803-10.
37. Attems J, Jellinger K, Thal DR, Van Nostrand W. Review: sporadic cerebral amyloid angiopathy. Neuropathology and applied neurobiology. 2011;37(1):75-93.
38. Hawkes CA, Hartig W, Kacza J, Schliebs R, Weller RO, Nicoll JA, et al. Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. Acta neuropathologica. 2011;121(4):431-43.
39. Tomonaga M. Cerebral amyloid angiopathy in the elderly. Journal of the American Geriatrics Society. 1981;29(4):151-7.
40. Yamada M, Tsukagoshi H, Otomo E, Hayakawa M. Cerebral amyloid angiopathy in the aged. Journal of neurology. 1987;234(6):371-6.
41. Chen YW, Lee MJ, Smith EE. Cerebral amyloid angiopathy in East and West. International journal of stroke : official journal of the International Stroke Society. 2010;5(5):403-11.
42. Arima H, Tzourio C, Anderson C, Woodward M, Bousser MG, MacMahon S, et al. Effects of perindopril-based lowering of blood pressure on intracerebral hemorrhage related to amyloid angiopathy: the PROGRESS trial. Stroke; a journal of cerebral circulation. 2010;41(2):394-6.
43. Ferreiro JA, Ansbacher LE, Vinters HV. Stroke related to cerebral amyloid angiopathy: the significance of systemic vascular disease. Journal of neurology. 1989;236(5):267-72.
44. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum: current outcomes and control in the community. JAMA : the journal of the American Medical Association. 2005;294(4):466-72.
45. Gregoire SM, Jager HR, Yousry TA, Kallis C, Brown MM, Werring DJ. Brain microbleeds as a potential risk factor for antiplatelet-related intracerebral haemorrhage: hospital-based, case-control study. Journal of neurology, neurosurgery, and psychiatry. 2010;81(6):679-84.
46. Soo YO, Yang SR, Lam WW, Wong A, Fan YH, Leung HH, et al. Risk vs benefit of anti-thrombotic therapy in ischaemic stroke patients with cerebral microbleeds. Journal of neurology. 2008;255(11):1679-86.
47. Ueno H, Naka H, Ohshita T, Kondo K, Nomura E, Ohtsuki T, et al. Association between cerebral microbleeds on T2*-weighted MR images and recurrent hemorrhagic stroke in patients treated with warfarin following ischemic stroke. AJNR American journal of neuroradiology. 2008;29(8):1483-6.
48. Lovelock CE, Cordonnier C, Naka H, Al-Shahi Salman R, Sudlow CL, Edinburgh Stroke Study G, et al. Antithrombotic drug use, cerebral microbleeds, and intracerebral hemorrhage: a systematic review of published and unpublished studies. Stroke; a journal of cerebral circulation. 2010;41(6):1222-8.

49. Rannikmae K, Samarasekera N, Martinez-Gonzalez NA, Al-Shahi Salman R, Sudlow CL. Genetics of cerebral amyloid angiopathy: systematic review and meta-analysis. Journal of neurology, neurosurgery, and psychiatry. 2013;84(8):901-8.
50. Rannikmae K, Kalaria RN, Greenberg SM, Chui HC, Schmitt FA, Samarasekera N, et al. APOE associations with severe CAA-associated vasculopathic changes: collaborative meta-analysis. Journal of neurology, neurosurgery, and psychiatry. 2014;85(3):300-5.
51. Greenberg SM, Rebeck GW, Vonsattel JP, Gomez-Isla T, Hyman BT. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. Annals of neurology. 1995;38(2):254-9.
52. Greenberg SM, Briggs ME, Hyman BT, Kokoris GJ, Takis C, Kanter DS, et al. Apolipoprotein E epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. Stroke; a journal of cerebral circulation. 1996;27(8):1333-7.
53. Biffi A, Sonni A, Anderson CD, Kissela B, Jagiella JM, Schmidt H, et al. Variants at APOE influence risk of deep and lobar intracerebral hemorrhage. Annals of neurology. 2010;68(6):934-43.
54. O'Donnell HC, Rosand J, Knudsen KA, Furie KL, Segal AZ, Chiu RI, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. The New England journal of medicine. 2000;342(4):240-5.
55. Yamada M. Cerebral amyloid angiopathy and gene polymorphisms. Journal of the neurological sciences. 2004;226(1-2):41-4.
56. Biffi A, Anderson CD, Jagiella JM, Schmidt H, Kissela B, Hansen BM, et al. APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. Lancet neurology. 2011;10(8):702-9.
57. Gudmundsson G, Hallgrimsson J, Jonasson TA, Bjarnason O. Hereditary cerebral haemorrhage with amyloidosis. Brain : a journal of neurology. 1972;95(2):387-404.
58. Okazaki H, Reagan TJ, Campbell RJ. Clinicopathologic studies of primary cerebral amyloid angiopathy. Mayo Clinic proceedings. 1979;54(1):22-31.
59. Tucker WS, Bilbao JM, Klodawsky H. Cerebral amyloid angiopathy and multiple intracerebral hematomas. Neurosurgery. 1980;7(6):611-4.
60. Wattendorff AR, Bots GT, Went LN, Endtz LJ. Familial cerebral amyloid angiopathy presenting as recurrent cerebral haemorrhage. Journal of the neurological sciences. 1982;55(2):121-35.
61. Finelli PF, Kessimian N, Bernstein PW. Cerebral amyloid angiopathy manifesting as recurrent intracerebral hemorrhage. Archives of neurology. 1984;41(3):330-3.
62. Samarasekera N, Smith C, Al-Shahi Salman R. The association between cerebral amyloid angiopathy and intracerebral haemorrhage: systematic review and meta-analysis. Journal of neurology, neurosurgery, and psychiatry. 2012;83(3):275-81.
63. Charidimou A, Imaizumi T, Moulin S, Biffi A, Samarasekera N, Yakushiji Y, et al. Brain hemorrhage recurrence, small vessel disease type, and cerebral microbleeds: A meta-analysis. Neurology. 2017;89(8):820-9.
64. Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP, Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. Annals of neurology. 1991;30(5):637-49.
65. Fisher CM. Lacunar strokes and infarcts: a review. Neurology. 1982;32(8):871-6.
66. Fisher CM. Lacunes: Small, Deep Cerebral Infarcts. Neurology. 1965;15:774-84.
67. Fisher CM. The arterial lesions underlying lacunes. Acta neuropathologica. 1968;12(1):1-15.
68. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. Lancet neurology. 2013;12(5):483-97.

69. Lammie GA. Hypertensive cerebral small vessel disease and stroke. Brain pathology. 2002;12(3):358-70.
70. Cole FM, Yates P. Intracerebral microaneurysms and small cerebrovascular lesions. Brain : a journal of neurology. 1967;90(4):759-68.
71. Feigin I, Prose P. Hypertensive fibrinoid arteritis of the brain and gross cerebral hemorrhage: a form of "hyalinosis". Archives of neurology. 1959;1:98-110.
72. Rosenblum WI. Cerebral hemorrhage produced by ruptured dissecting aneurysm in miliary aneurysm. Annals of neurology. 2003;54(3):376-8.
73. Fisher CM. Pathological observations in hypertensive cerebral hemorrhage. Journal of neuropathology and experimental neurology. 1971;30(3):536-50.
74. Takebayashi S, Kaneko M. Electron microscopic studies of ruptured arteries in hypertensive intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 1983;14(1):28-36.
75. Beilin LJ, Goldby FS, Mohring J. High arterial pressure versus humoral factors in the pathogenesis of the vascular lesions of malignant hypertension. Clinical science and molecular medicine. 1977;52(2):111-7.
76. Brott T, Thalinger K, Hertzberg V. Hypertension as a risk factor for spontaneous intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 1986;17(6):1078-83.
77. Bahemuka M. Primary intracerebral hemorrhage and heart weight: a clinicopathologic case-control review of 218 patients. Stroke; a journal of cerebral circulation. 1987;18(2):531-6.
78. Rosenblum WI. Miliary aneurysms and "fibrinoid" degeneration of cerebral blood vessels. Human pathology. 1977;8(2):133-9.
79. Lammie GA, Brannan F, Slattery J, Warlow C. Nonhypertensive cerebral small-vessel disease. An autopsy study. Stroke; a journal of cerebral circulation. 1997;28(11):2222-9.
80. Fernando MS, Simpson JE, Matthews F, Brayne C, Lewis CE, Barber R, et al. White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury. Stroke; a journal of cerebral circulation. 2006;37(6):1391-8.
81. Moody DM, Thore CR, Anstrom JA, Challa VR, Langefeld CD, Brown WR. Quantification of afferent vessels shows reduced brain vascular density in subjects with leukoaraiosis. Radiology. 2004;233(3):883-90.
82. Ryan DJ, Byrne S, Dunne R, Harmon M, Harbison J. White matter disease and an incomplete circle of Willis. International journal of stroke : official journal of the International Stroke Society. 2013.
83. Alosco ML, Brickman AM, Spitznagel MB, Garcia SL, Narkhede A, Griffith EY, et al. Cerebral perfusion is associated with white matter hyperintensities in older adults with heart failure. Congestive heart failure. 2013;19(4):E29-34.
84. Duan W, Gui L, Zhou Z, Liu Y, Tian H, Chen JF, et al. Adenosine A2A receptor deficiency exacerbates white matter lesions and cognitive deficits induced by chronic cerebral hypoperfusion in mice. Journal of the neurological sciences. 2009;285(1-2):39-45.
85. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovascular psychiatry and neurology. 2012;2012:367516.
86. Falcone GJ, Biffi A, Devan WJ, Brouwers HB, Anderson CD, Valant V, et al. Burden of blood pressure-related alleles is associated with larger hematoma volume and worse outcome in intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2013;44(2):321-6.
87. Park JH, Seo SW, Kim C, Kim GH, Noh HJ, Kim ST, et al. Pathogenesis of cerebral microbleeds: In vivo imaging of amyloid and subcortical ischemic small vessel disease in 226 individuals with cognitive impairment. Annals of neurology. 2013;73(5):584-93.
88. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al. Cerebral microbleeds: a guide to detection and interpretation. Lancet neurology. 2009;8(2):165-74.

89. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR American journal of neuroradiology. 1999;20(4):637-42.
90. Tanaka A, Ueno Y, Nakayama Y, Takano K, Takebayashi S. Small chronic hemorrhages and ischemic lesions in association with spontaneous intracerebral hematomas. Stroke; a journal of cerebral circulation. 1999;30(8):1637-42.
91. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology. 2001;56(4):537-9.
92. Reijmer YD, Fotiadis P, Martinez-Ramirez S, Salat DH, Schultz A, Shoamanesh A, et al. Structural network alterations and neurological dysfunction in cerebral amyloid angiopathy. Brain : a journal of neurology. 2014.
93. Shoamanesh A, Kwok CS, Benavente O. Cerebral microbleeds: histopathological correlation of neuroimaging. Cerebrovascular diseases. 2011;32(6):528-34.
94. Janaway BM, Simpson JE, Hoggard N, Highley JR, Forster G, Drew D, et al. Brain haemosiderin in older people: pathological evidence for an ischaemic origin of magnetic resonance imaging (MRI) microbleeds. Neuropathology and applied neurobiology. 2014;40(3):258-69.
95. Grutzendler J, Murikinati S, Hiner B, Ji L, Lam CK, Yoo T, et al. Angiophagy prevents early embolus washout but recanalizes microvessels through embolus extravasation. Science translational medicine. 2014;6(226):226ra31.
96. Tanskanen M, Makela M, Myllykangas L, Rastas S, Sulkava R, Paetau A. Intracerebral hemorrhage in the oldest old: a population-based study (vantaa 85+). Frontiers in neurology. 2012;3:103.
97. Fisher M. Cerebral microbleeds: where are we now? Neurology. 2014;83(15):1304-5.
98. van Veluw SJ, Biessels GJ, Klijn CJ, Rozemuller AJ. Heterogeneous histopathology of cortical microbleeds in cerebral amyloid angiopathy. Neurology. 2016;86(9):867-71.
99. Charidimou A, Krishnan A, Werring DJ, Rolf Jager H. Cerebral microbleeds: a guide to detection and clinical relevance in different disease settings. Neuroradiology. 2013;55(6):655-74.
100. Vernooij MW, van der Lugt A, Ikram MA, Wielopolski PA, Niessen WJ, Hofman A, et al. Prevalence and risk factors of cerebral microbleeds: the Rotterdam Scan Study. Neurology. 2008;70(14):1208-14.
101. Maxwell SS, Jackson CA, Paternoster L, Cordonnier C, Thijs V, Al-Shahi Salman R, et al. Genetic associations with brain microbleeds: Systematic review and meta-analyses. Neurology. 2011;77(2):158-67.
102. Schilling S, DeStefano AL, Sachdev PS, Choi SH, Mather KA, DeCarli CD, et al. APOE genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. Neurology. 2013;81(3):292-300.
103. Dierksen GA, Skehan ME, Khan MA, Jeng J, Nandigam RN, Becker JA, et al. Spatial relation between microbleeds and amyloid deposits in amyloid angiopathy. Annals of neurology. 2010;68(4):545-8.
104. Lee SH, Bae HJ, Kwon SJ, Kim H, Kim YH, Yoon BW, et al. Cerebral microbleeds are regionally associated with intracerebral hemorrhage. Neurology. 2004;62(1):72-6.
105. Roob G, Lechner A, Schmidt R, Flooh E, Hartung HP, Fazekas F. Frequency and location of microbleeds in patients with primary intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2000;31(11):2665-9.
106. van Rooden S, van der Grond J, van den Boom R, Haan J, Linn J, Greenberg SM, et al. Descriptive analysis of the Boston criteria applied to a Dutch-type cerebral amyloid angiopathy population. Stroke; a journal of cerebral circulation. 2009;40(9):3022-7.

107. Charidimou A, Jaunmuktane Z, Baron JC, Burnell M, Varlet P, Peeters A, et al. White matter perivascular spaces: an MRI marker in pathology-proven cerebral amyloid angiopathy? Neurology. 2014;82(1):57-62.
108. Akoudad S, Portegies ML, Koudstaal PJ, Hofman A, van der Lugt A, Ikram MA, et al. Cerebral Microbleeds Are Associated With an Increased Risk of Stroke: The Rotterdam Study. Circulation. 2015;132(6):509-16.
109. Gregoire SM, Brown MM, Kallis C, Jager HR, Yousry TA, Werring DJ. MRI detection of new microbleeds in patients with ischemic stroke: five-year cohort follow-up study. Stroke; a journal of cerebral circulation. 2010;41(1):184-6.
110. Pasquini M, Benedictus MR, Boulouis G, Rossi C, Dequatre-Ponchelle N, Cordonnier C. Incident Cerebral Microbleeds in a Cohort of Intracerebral Hemorrhage. Stroke; a journal of cerebral circulation. 2016;47(3):689-94.
111. Martinez-Ramirez S, Romero JR, Shoamanesh A, McKee AC, Van Etten E, Pontes-Neto O, et al. Diagnostic value of lobar microbleeds in individuals without intracerebral hemorrhage. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2015.
112. Wilson D, Werring DJ. Establishing the "meaning" of microbleeds: Clinical context or lobar microbleed burden? Alzheimer's & dementia : the journal of the Alzheimer's Association. 2016;12(1):85-6.
113. Bokura H, Saika R, Yamaguchi T, Nagai A, Oguro H, Kobayashi S, et al. Microbleeds are associated with subsequent hemorrhagic and ischemic stroke in healthy elderly individuals. Stroke; a journal of cerebral circulation. 2011;42(7):1867-71.
114. van Etten ES, Auriel E, Haley KE, Ayres AM, Vashkevich A, Schwab KM, et al. Incidence of symptomatic hemorrhage in patients with lobar microbleeds. Stroke; a journal of cerebral circulation. 2014;45(8):2280-5.
115. Liu S, Li C. Antiplatelet Drug Use and Cerebral Microbleeds: A Meta-analysis of Published Studies. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2015;24(10):2236-44.
116. Wobith M, Mayer C, Belke M, Haag A, Gerstner A, Teepker M, et al. Predictors of New Cerebral Microbleeds in Patients with Antiplatelet Drug Therapy. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2016;25(7):1671-7.
117. O'Donnell MJ, Eikelboom JW, Yusuf S, Diener HC, Hart RG, Smith EE, et al. Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study. American heart journal. 2016;178:145-50.
118. Horstmann S, Mohlenbruch M, Wegele C, Rizos T, Laible M, Rauch G, et al. Prevalence of atrial fibrillation and association of previous antithrombotic treatment in patients with cerebral microbleeds. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2015;22(10):1355-62.
119. Charidimou A, Kakar P, Fox Z, Werring DJ. Cerebral microbleeds and recurrent stroke risk: systematic review and meta-analysis of prospective ischemic stroke and transient ischemic attack cohorts. Stroke; a journal of cerebral circulation. 2013;44(4):995-1001.
120. Haji S, Planchard R, Zubair A, Graff-Radford J, Rydberg C, Brown RD, Jr., et al. The clinical relevance of cerebral microbleeds in patients with cerebral ischemia and atrial fibrillation. Journal of neurology. 2016;263(2):238-44.
121. Song TJ, Kim J, Song D, Nam HS, Kim YD, Lee HS, et al. Association of cerebral microbleeds with mortality in stroke patients having atrial fibrillation. Neurology. 2014;83(15):1308-15.
122. Song TJ, Kim J, Lee HS, Nam CM, Nam HS, Heo JH, et al. The frequency of cerebral microbleeds increases with CHADS(2) scores in stroke patients with non-valvular atrial fibrillation. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2013;20(3):502-8.

123. Charidimou A, Inamura S, Nomura T, Kanno A, Kim SN, Imaizumi T. Cerebral microbleeds and white matter hyperintensities in cardioembolic stroke patients due to atrial fibrillation: single-centre longitudinal study. Journal of the neurological sciences. 2016;369:263-7.
124. Viswanathan A, Rakich SM, Engel C, Snider R, Rosand J, Greenberg SM, et al. Antiplatelet use after intracerebral hemorrhage. Neurology. 2006;66(2):206-9.
125. Biffi A, Halpin A, Towfighi A, Gilson A, Busl K, Rost N, et al. Aspirin and recurrent intracerebral hemorrhage in cerebral amyloid angiopathy. Neurology. 2010;75(8):693-8.
126. Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke; a journal of cerebral circulation. 2004;35(6):1415-20.
127. Jeon SB, Kang DW, Cho AH, Lee EM, Choi CG, Kwon SU, et al. Initial microbleeds at MR imaging can predict recurrent intracerebral hemorrhage. Journal of neurology. 2007;254(4):508-12.
128. Eckman MH, Rosand J, Knudsen KA, Singer DE, Greenberg SM. Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. Stroke; a journal of cerebral circulation. 2003;34(7):1710-6.
129. Kuramatsu JB, Gerner ST, Schellinger PD, Glahn J, Endres M, Sobesky J, et al. Anticoagulant reversal, blood pressure levels, and anticoagulant resumption in patients with anticoagulation-related intracerebral hemorrhage. JAMA : the journal of the American Medical Association. 2015;313(8):824-36.
130. Nielsen PB, Larsen TB, Skjoth F, Gorst-Rasmussen A, Rasmussen LH, Lip GY. Restarting Anticoagulant Treatment After Intracranial Hemorrhage in Patients With Atrial Fibrillation and the Impact on Recurrent Stroke, Mortality, and Bleeding: A Nationwide Cohort Study. Circulation. 2015;132(6):517-25.
131. Vestergaard AS, Skjoth F, Lip GY, Larsen TB. Effect of Anticoagulation on Hospitalization Costs After Intracranial Hemorrhage in Atrial Fibrillation: A Registry Study. Stroke; a journal of cerebral circulation. 2016;47(4):979-85.
132. Charidimou A, Linn J, Vernooij MW, Opherk C, Akoudad S, Baron JC, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. Brain : a journal of neurology. 2015;138(Pt 8):2126-39.
133. Wilson D, Chatterjee F, Farmer SF, Rudge P, McCarron MO, Cowley P, et al. Infratentorial superficial siderosis: Classification, diagnostic criteria, and rational investigation pathway. Annals of neurology. 2017;81(3):333-43.
134. Raposo N, Viguier A, Cuvinciuc V, Calviere L, Cognard C, Bonneville F, et al. Cortical subarachnoid haemorrhage in the elderly: a recurrent event probably related to cerebral amyloid angiopathy. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2011;18(4):597-603.
135. Kumar S, Goddeau RP, Jr., Selim MH, Thomas A, Schlaug G, Alhazzani A, et al. Atraumatic convexal subarachnoid hemorrhage: clinical presentation, imaging patterns, and etiologies. Neurology. 2010;74(11):893-9.
136. Charidimou A, Jager RH, Fox Z, Peeters A, Vandermeeren Y, Laloux P, et al. Prevalence and mechanisms of cortical superficial siderosis in cerebral amyloid angiopathy. Neurology. 2013;81(7):626-32.
137. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology. 2010;74(17):1346-50.
138. Linn J, Herms J, Dichgans M, Bruckmann H, Fesl G, Freilinger T, et al. Subarachnoid hemosiderosis and superficial cortical hemosiderosis in cerebral amyloid angiopathy. AJNR American journal of neuroradiology. 2008;29(1):184-6.

139. Wilson D, Hostettler IC, Ambler G, Banerjee G, Jager HR, Werring DJ. Convexity subarachnoid haemorrhage has a high risk of intracerebral haemorrhage in suspected cerebral amyloid angiopathy. Journal of neurology. 2017;264(4):664-73.
140. Vernooij MW, Ikram MA, Hofman A, Krestin GP, Breteler MM, van der Lugt A. Superficial siderosis in the general population. Neurology. 2009;73(3):202-5.
141. Pichler M, Vemuri P, Rabinstein AA, Aakre J, Flemming KD, Brown RD, Jr., et al. Prevalence and Natural History of Superficial Siderosis: A Population-Based Study. Stroke; a journal of cerebral circulation. 2017;48(12):3210-4.
142. Roch JA, Nighoghossian N, Hermier M, Cakmak S, Picot M, Honnorat J, et al. Transient neurologic symptoms related to cerebral amyloid angiopathy: usefulness of T2*-weighted imaging. Cerebrovascular diseases. 2005;20(5):412-4.
143. Charidimou A, Peeters A, Fox Z, Gregoire SM, Vandermeeren Y, Laloux P, et al. Spectrum of transient focal neurological episodes in cerebral amyloid angiopathy: multicentre magnetic resonance imaging cohort study and meta-analysis. Stroke; a journal of cerebral circulation. 2012;43(9):2324-30.
144. Linn J, Wollenweber FA, Lummel N, Bochmann K, Pfefferkorn T, Gschwendtner A, et al. Superficial siderosis is a warning sign for future intracranial hemorrhage. Journal of neurology. 2013;260(1):176-81.
145. Charidimou A, Peeters AP, Jager R, Fox Z, Vandermeeren Y, Laloux P, et al. Cortical superficial siderosis and intracerebral hemorrhage risk in cerebral amyloid angiopathy. Neurology. 2013;81(19):1666-73.
146. Roongpiboonsopit D, Charidimou A, William CM, Lauer A, Falcone GJ, Martinez-Ramirez S, et al. Cortical superficial siderosis predicts early recurrent lobar hemorrhage. Neurology. 2016;87(18):1863-70.
147. Charidimou A, Boulouis G, Roongpiboonsopit D, Auriel E, Pasi M, Haley K, et al. Cortical superficial siderosis multifocality in cerebral amyloid angiopathy: A prospective study. Neurology. 2017;89(21):2128-35.
148. Charidimou A, Boulouis G, Xiong L, Jessel MJ, Roongpiboonsopit D, Ayres A, et al. Cortical superficial siderosis and first-ever cerebral hemorrhage in cerebral amyloid angiopathy. Neurology. 2017;88(17):1607-14.
149. Hachinski VC, Potter P, Merskey H. Leuko-araiosis. Archives of neurology. 1987;44(1):21-3.
150. Gouw AA, Seewann A, van der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, et al. Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. Journal of neurology, neurosurgery, and psychiatry. 2011;82(2):126-35.
151. Pantoni L GP. Cerebral small vessel disease: Cambridge University Press; 2014.
152. Vinters HV, Gilbert JJ. Cerebral amyloid angiopathy: incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. Stroke; a journal of cerebral circulation. 1983;14(6):924-8.
153. Masuda J, Tanaka K, Ueda K, Omae T. Autopsy study of incidence and distribution of cerebral amyloid angiopathy in Hisayama, Japan. Stroke; a journal of cerebral circulation. 1988;19(2):205-10.
154. Rosand J, Muzikansky A, Kumar A, Wisco JJ, Smith EE, Betensky RA, et al. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. Annals of neurology. 2005;58(3):459-62.
155. Smith EE. Leukoaraiosis and stroke. Stroke; a journal of cerebral circulation. 2010;41(10 Suppl):S139-43.
156. Smith EE, Nandigam KR, Chen YW, Jeng J, Salat D, Halpin A, et al. MRI markers of small vessel disease in lobar and deep hemispheric intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2010;41(9):1933-8.

157. Charidimou A, Boulouis G, Haley K, Auriel E, van Etten ES, Fotiadis P, et al. White matter hyperintensity patterns in cerebral amyloid angiopathy and hypertensive arteriopathy. Neurology. 2016;86(6):505-11.
158. Kongbunkiat K, Wilson D, Kasemsap N, Tiamkao S, Jichi F, Palumbo V, et al. Leukoaraiosis, intracerebral hemorrhage, and functional outcome after acute stroke thrombolysis. Neurology. 2017;88(7):638-45.
159. Smith EE, Gurol ME, Eng JA, Engel CR, Nguyen TN, Rosand J, et al. White matter lesions, cognition, and recurrent hemorrhage in lobar intracerebral hemorrhage. Neurology. 2004;63(9):1606-12.
160. Gregoire SM, Charidimou A, Gadapa N, Dolan E, Antoun N, Peeters A, et al. Acute ischaemic brain lesions in intracerebral haemorrhage: multicentre cross-sectional magnetic resonance imaging study. Brain : a journal of neurology. 2011;134(Pt 8):2376-86.
161. Auriel E, Gurol ME, Ayres A, Dumas AP, Schwab KM, Vashkevich A, et al. Characteristic distributions of intracerebral hemorrhage-associated diffusion-weighted lesions. Neurology. 2012;79(24):2335-41.
162. Kang DW, Han MK, Kim HJ, Yun SC, Jeon SB, Bae HJ, et al. New ischemic lesions coexisting with acute intracerebral hemorrhage. Neurology. 2012;79(9):848-55.
163. Menon RS, Burgess RE, Wing JJ, Gibbons MC, Shara NM, Fernandez S, et al. Predictors of highly prevalent brain ischemia in intracerebral hemorrhage. Annals of neurology. 2012;71(2):199-205.
164. Shoamanesh A, Catanese L, Sakai O, Pikula A, Kase CS. Diffusion-weighted imaging hyperintensities in intracerebral hemorrhage: microinfarcts or microbleeds? Annals of neurology. 2013;73(6):795-6.
165. Arsava EM, Kayim-Yildiz O, Oguz KK, Akpinar E, Topcuoglu MA. Elevated admission blood pressure and acute ischemic lesions in spontaneous intracerebral hemorrhage. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2013;22(3):250-4.
166. Abbott NJ. Evidence for bulk flow of brain interstitial fluid: significance for physiology and pathology. Neurochemistry international. 2004;45(4):545-52.
167. Marin-Padilla M, Knopman DS. Developmental aspects of the intracerebral microvasculature and perivascular spaces: insights into brain response to late-life diseases. Journal of neuropathology and experimental neurology. 2011;70(12):1060-9.
168. Weller RO, Djuanda E, Yow HY, Carare RO. Lymphatic drainage of the brain and the pathophysiology of neurological disease. Acta neuropathologica. 2009;117(1):1-14.
169. Arbel-Ornath M, Hudry E, Eikermann-Haerter K, Hou S, Gregory JL, Zhao L, et al. Interstitial fluid drainage is impaired in ischemic stroke and Alzheimer's disease mouse models. Acta neuropathologica. 2013;126(3):353-64.
170. Young VG, Halliday GM, Kril JJ. Neuropathologic correlates of white matter hyperintensities. Neurology. 2008;71(11):804-11.
171. Potter GM, Doubal FN, Jackson CA, Chappell FM, Sudlow CL, Dennis MS, et al. Enlarged perivascular spaces and cerebral small vessel disease. International journal of stroke : official journal of the International Stroke Society. 2013.
172. Doubal FN, MacLullich AM, Ferguson KJ, Dennis MS, Wardlaw JM. Enlarged perivascular spaces on MRI are a feature of cerebral small vessel disease. Stroke; a journal of cerebral circulation. 2010;41(3):450-4.
173. Rouhl RP, van Oostenbrugge RJ, Knottnerus IL, Staals JE, Lodder J. Virchow-Robin spaces relate to cerebral small vessel disease severity. Journal of neurology. 2008;255(5):692-6.
174. Charidimou A, Meegahage R, Fox Z, Peeters A, Vandermeeren Y, Laloux P, et al. Enlarged perivascular spaces as a marker of underlying arteriopathy in intracerebral haemorrhage: a

multicentre MRI cohort study. Journal of neurology, neurosurgery, and psychiatry. 2013;84(6):624-9.
175. Schrag M, McAuley G, Pomakian J, Jiffry A, Tung S, Mueller C, et al. Correlation of hypointensities in susceptibility-weighted images to tissue histology in dementia patients with cerebral amyloid angiopathy: a postmortem MRI study. Acta neuropathologica. 2010;119(3):291-302.
176. Poels MM, Vernooij MW, Ikram MA, Hofman A, Krestin GP, van der Lugt A, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. Stroke; a journal of cerebral circulation. 2010;41(10 Suppl):S103-6.
177. Yakushiji Y, Yokota C, Yamada N, Kuroda Y, Minematsu K. Clinical characteristics by topographical distribution of brain microbleeds, with a particular emphasis on diffuse microbleeds. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2011;20(3):214-21.
178. Smith EE, Schneider JA, Wardlaw JM, Greenberg SM. Cerebral microinfarcts: the invisible lesions. Lancet neurology. 2012;11(3):272-82.
179. van den Brink H, Zwiers A, Switzer AR, Charlton A, McCreary CR, Goodyear BG, et al. Cortical Microinfarcts on 3T Magnetic Resonance Imaging in Cerebral Amyloid Angiopathy: Relations With Other Magnetic Resonance Imaging Markers of Cerebral Amyloid Angiopathy and Cognition. Stroke; a journal of cerebral circulation. 2018.
180. van Veluw SJ, Zwanenburg JJ, Engelen-Lee J, Spliet WG, Hendrikse J, Luijten PR, et al. In vivo detection of cerebral cortical microinfarcts with high-resolution 7T MRI. J Cereb Blood Flow Metab. 2013;33(3):322-9.
181. Auriel E, Westover MB, Bianchi MT, Reijmer Y, Martinez-Ramirez S, Ni J, et al. Estimating Total Cerebral Microinfarct Burden From Diffusion-Weighted Imaging. Stroke; a journal of cerebral circulation. 2015;46(8):2129-35.
182. Arvanitakis Z, Capuano AW, Leurgans SE, Buchman AS, Bennett DA, Schneider JA. The Relationship of Cerebral Vessel Pathology to Brain Microinfarcts. Brain pathology. 2017;27(1):77-85.
183. Kovari E, Herrmann FR, Gold G, Hof PR, Charidimou A. Association of cortical microinfarcts and cerebral small vessel pathology in the ageing brain. Neuropathology and applied neurobiology. 2017;43(6):505-13.
184. Hilal S, Sikking E, Shaik MA, Chan QL, van Veluw SJ, Vrooman H, et al. Cortical cerebral microinfarcts on 3T MRI: A novel marker of cerebrovascular disease. Neurology. 2016;87(15):1583-90.
185. Gwon JG, Kwon TW, Cho YP, Kang DW, Han Y, Noh M. Analysis of Risk Factors for Cerebral Microinfarcts after Carotid Endarterectomy and the Relevance of Delayed Cerebral Infarction. J Clin Neurol. 2017;13(1):32-7.
186. Hilal S, Chai YL, van Veluw S, Shaik MA, Ikram MK, Venketasubramanian N, et al. Association Between Subclinical Cardiac Biomarkers and Clinically Manifest Cardiac Diseases With Cortical Cerebral Microinfarcts. JAMA neurology. 2017;74(4):403-10.
187. Wang Z, van Veluw SJ, Wong A, Liu W, Shi L, Yang J, et al. Risk Factors and Cognitive Relevance of Cortical Cerebral Microinfarcts in Patients With Ischemic Stroke or Transient Ischemic Attack. Stroke; a journal of cerebral circulation. 2016;47(10):2450-5.
188. Imaizumi T, Inamura S, Kohama I, Yoshifuji K, Nomura T, Komatsu K. Nascent lobar microbleeds and stroke recurrences. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2014;23(4):610-7.
189. Boulanger JM, Coutts SB, Eliasziw M, Gagnon AJ, Simon JE, Subramaniam S, et al. Cerebral microhemorrhages predict new disabling or fatal strokes in patients with acute ischemic stroke or transient ischemic attack. Stroke; a journal of cerebral circulation. 2006;37(3):911-4.

190. Thijs V, Lemmens R, Schoofs C, Gorner A, Van Damme P, Schrooten M, et al. Microbleeds and the risk of recurrent stroke. Stroke; a journal of cerebral circulation. 2010;41(9):2005-9.
191. Lim JS, Hong KS, Kim GM, Bang OY, Bae HJ, Kwon HM, et al. Cerebral microbleeds and early recurrent stroke after transient ischemic attack: results from the Korean Transient Ischemic Attack Expression Registry. JAMA neurology. 2015;72(3):301-8.
192. Fluri F, Jax F, Amort M, Wetzel SG, Lyrer PA, Katan M, et al. Significance of microbleeds in patients with transient ischaemic attack. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2012;19(3):522-4.
193. Akoudad S, Ikram MA, Koudstaal PJ, Hofman A, Niessen WJ, Greenberg SM, et al. Cerebral microbleeds are associated with the progression of ischemic vascular lesions. Cerebrovascular diseases. 2014;37(5):382-8.
194. Huang Y, Cheng Y, Wu J, Li Y, Xu E, Hong Z, et al. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. Lancet neurology. 2008;7(6):494-9.
195. Kwa VI, Algra A, Brundel M, Bouvy W, Kappelle LJ, Group MS. Microbleeds as a predictor of intracerebral haemorrhage and ischaemic stroke after a TIA or minor ischaemic stroke: a cohort study. BMJ open. 2013;3(5).
196. Naka H, Nomura E, Takahashi T, Wakabayashi S, Mimori Y, Kajikawa H, et al. Combinations of the presence or absence of cerebral microbleeds and advanced white matter hyperintensity as predictors of subsequent stroke types. AJNR American journal of neuroradiology. 2006;27(4):830-5.
197. Fan YH, Zhang L, Lam WW, Mok VC, Wong KS. Cerebral microbleeds as a risk factor for subsequent intracerebral hemorrhages among patients with acute ischemic stroke. Stroke; a journal of cerebral circulation. 2003;34(10):2459-62.
198. Mok VC, Lau AY, Wong A, Lam WW, Chan A, Leung H, et al. Long-term prognosis of Chinese patients with a lacunar infarct associated with small vessel disease: a five-year longitudinal study. International journal of stroke : official journal of the International Stroke Society. 2009;4(2):81-8.
199. Imaizumi T, Horita Y, Hashimoto Y, Niwa J. Dotlike hemosiderin spots on T2*-weighted magnetic resonance imaging as a predictor of stroke recurrence: a prospective study. Journal of neurosurgery. 2004;101(6):915-20.
200. Wang DN, Hou XW, Yang BW, Lin Y, Shi JP, Wang N. Quantity of Cerebral Microbleeds, Antiplatelet Therapy, and Intracerebral Hemorrhage Outcomes: A Systematic Review and Meta-analysis. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association. 2015.
201. Antithrombotic Trialists C. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. Bmj. 2002;324(7329):71-86.
202. Stehling C, Wersching H, Kloska SP, Kirchhof P, Ring J, Nassenstein I, et al. Detection of asymptomatic cerebral microbleeds: a comparative study at 1.5 and 3.0 T. Academic radiology. 2008;15(7):895-900.
203. Gregoire SM, Werring DJ, Chaudhary UJ, Thornton JS, Brown MM, Yousry TA, et al. Choice of echo time on GRE T2*-weighted MRI influences the classification of brain microbleeds. Clinical radiology. 2010;65(5):391-4.
204. Cheng AL, Batool S, McCreary CR, Lauzon ML, Frayne R, Goyal M, et al. Susceptibility-weighted imaging is more reliable than T2*-weighted gradient-recalled echo MRI for detecting microbleeds. Stroke; a journal of cerebral circulation. 2013;44(10):2782-6.
205. Shams S, Martola J, Cavallin L, Granberg T, Shams M, Aspelin P, et al. SWI or T2*: which MRI sequence to use in the detection of cerebral microbleeds? The Karolinska Imaging Dementia Study. AJNR American journal of neuroradiology. 2015;36(6):1089-95.

206. Cordonnier C, Al-Shahi Salman R, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain : a journal of neurology. 2007;130(Pt 8):1988-2003.
207. Gregoire SM, Chaudhary UJ, Brown MM, Yousry TA, Kallis C, Jager HR, et al. The Microbleed Anatomical Rating Scale (MARS): reliability of a tool to map brain microbleeds. Neurology. 2009;73(21):1759-66.
208. Charidimou A, Wilson D, Shakeshaft C, Ambler G, White M, Cohen H, et al. The Clinical Relevance of Microbleeds in Stroke study (CROMIS-2): rationale, design, and methods. International journal of stroke : official journal of the International Stroke Society. 2015.
209. Rockson SG, Albers GW. Comparing the guidelines: anticoagulation therapy to optimize stroke prevention in patients with atrial fibrillation. Journal of the American College of Cardiology. 2004;43(6):929-35.
210. Dogliotti A, Paolasso E, Giugliano RP. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients. Heart. 2014;100(5):396-405.
211. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-67.
212. Dowlatshahi D, Butcher KS, Asdaghi N, Nahirniak S, Bernbaum ML, Giulivi A, et al. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. Stroke; a journal of cerebral circulation. 2012;43(7):1812-7.
213. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138(5):1093-100.
214. Gage BF, Yan Y, Milligan PE, Waterman AD, Culverhouse R, Rich MW, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). American heart journal. 2006;151(3):713-9.
215. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, et al. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. Journal of the American College of Cardiology. 2011;58(4):395-401.
216. Charidimou A, Karayiannis C, Song TJ, Orken DN, Thijs V, Lemmens R, et al. Brain microbleeds, anticoagulation, and hemorrhage risk: Meta-analysis in stroke patients with AF. Neurology. 2017.
217. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjogren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke; a journal of cerebral circulation. 2001;32(6):1318-22.
218. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR Am J Roentgenol. 1987;149(2):351-6.
219. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. Journal of thrombosis and haemostasis : JTH. 2005;3(4):692-4.
220. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. Eur Heart J. 2012;33(12):1500-10.
221. Steyerberg EW. New York: Springer. 2009. [cited 2009].
222. Tibshirani R. The lasso method for variable selection in the Cox model. Stat Med. 1997;16(4):385-95.
223. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med. 1999;18(6):681-94.

224. Charidimou A, Boulouis G, Shams S, Calvet D, Shoamanesh A, International M-MI. Intracerebral haemorrhage risk in microbleed-positive ischaemic stroke patients with atrial fibrillation: Preliminary meta-analysis of cohorts and anticoagulation decision schema. Journal of the neurological sciences. 2017;378:102-9.
225. Wilson D, Werring DJ. Antithrombotic therapy in patients with cerebral microbleeds. Curr Opin Neurol. 2017;30(1):38-47.
226. Jin C, Li G, Rexrode KM, Gurol ME, Yuan X, Hui Y, et al. Prospective Study of Fasting Blood Glucose and Intracerebral Hemorrhagic Risk. Stroke; a journal of cerebral circulation. 2017.
227. Poli D, Antonucci E, Marcucci R, Fatini C, Alterini B, Mannini L, et al. Risk of bleeding in very old atrial fibrillation patients on warfarin: relationship with ageing and CHADS2 score. Thrombosis research. 2007;121(3):347-52.
228. Wilson D, Charidimou A, Ambler G, Fox ZV, Gregoire S, Rayson P, et al. Recurrent stroke risk and cerebral microbleed burden in ischemic stroke and TIA: A meta-analysis. Neurology. 2016.
229. Cordonnier C, Potter GM, Jackson CA, Doubal F, Keir S, Sudlow CL, et al. improving interrater agreement about brain microbleeds: development of the Brain Observer MicroBleed Scale (BOMBS). Stroke; a journal of cerebral circulation. 2009;40(1):94-9.
230. Foulkes MA, Wolf PA, Price TR, Mohr JP, Hier DB. The Stroke Data Bank: design, methods, and baseline characteristics. Stroke; a journal of cerebral circulation. 1988;19(5):547-54.
231. Delgado Almandoz JE, Jagadeesan BD, Moran CJ, Cross DT, 3rd, Zipfel GJ, Lee JM, et al. Independent validation of the secondary intracerebral hemorrhage score with catheter angiography and findings of emergent hematoma evacuation. Neurosurgery. 2012;70(1):131-40; discussion 40.
232. van Asch CJ, Velthuis BK, Greving JP, van Laar PJ, Rinkel GJ, Algra A, et al. External validation of the secondary intracerebral hemorrhage score in The Netherlands. Stroke; a journal of cerebral circulation. 2013;44(10):2904-6.
233. Delgado Almandoz JE, Schaefer PW, Forero NP, Falla JR, Gonzalez RG, Romero JM. Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraparenchymal cerebral hemorrhage. AJNR American journal of neuroradiology. 2009;30(6):1213-21.
234. Charidimou A, Schmitt A, Wilson D, Yakushiji Y, Gregoire S, Fox Z, et al. The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS): development and assessment of reliability" Journal of the neurological sciences.In press.
235. Steyerberg EW. Clinical Prediction Models. New York: Springer; 2009.
236. Josephson CB, White PM, Krishan A, Al-Shahi Salman R. Computed tomography angiography or magnetic resonance angiography for detection of intracranial vascular malformations in patients with intracerebral haemorrhage. The Cochrane database of systematic reviews. 2014;9:CD009372.
237. van Asch CJ, Velthuis BK, Rinkel GJ, Algra A, de Kort GA, Witkamp TD, et al. Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. Bmj. 2015;351:h5762.
238. Lummel N, Lutz J, Bruckmann H, Linn J. The value of magnetic resonance imaging for the detection of the bleeding source in non-traumatic intracerebral haemorrhages: a comparison with conventional digital subtraction angiography. Neuroradiology. 2012;54(7):673-80.
239. Romero JM, Artunduaga M, Forero NP, Delgado J, Sarfaraz K, Goldstein JN, et al. Accuracy of CT angiography for the diagnosis of vascular abnormalities causing intraparenchymal hemorrhage in young patients. Emergency radiology. 2009;16(3):195-201.

240. Wong GK, Siu DY, Abrigo JM, Poon WS, Tsang FC, Zhu XL, et al. Computed tomographic angiography and venography for young or nonhypertensive patients with acute spontaneous intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2011;42(1):211-3.
241. Yoon DY, Chang SK, Choi CS, Kim WK, Lee JH. Multidetector row CT angiography in spontaneous lobar intracerebral hemorrhage: a prospective comparison with conventional angiography. AJNR American journal of neuroradiology. 2009;30(5):962-7.
242. Yeung R, Ahmad T, Aviv RI, de Tilly LN, Fox AJ, Symons SP. Comparison of CTA to DSA in determining the etiology of spontaneous ICH. The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques. 2009;36(2):176-80.
243. Wattjes MP, Henneman WJ, van der Flier WM, de Vries O, Traber F, Geurts JJ, et al. Diagnostic imaging of patients in a memory clinic: comparison of MR imaging and 64-detector row CT. Radiology. 2009;253(1):174-83.
244. Horstmann S, Rizos T, Jenetzky E, Gumbinger C, Hacke W, Veltkamp R. Prevalence of atrial fibrillation in intracerebral hemorrhage. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2014;21(4):570-6.
245. Tai SY, Lin FC, Lee CY, Chang CJ, Wu MT, Chien CY. Statin use after intracerebral hemorrhage: a 10-year nationwide cohort study. Brain Behav. 2016;6(8):e00487.
246. Jhuo SJ, Tsai WC, Lin TH, Voon WC, Lai WT, Sheu SH. Statin Dose and the Risk of Intracerebral Hemorrhage: A Population-Based Longitudinal Study in Taiwan. Acta Cardiol Sin. 2016;32(1):23-30.
247. Goldstein LB, Amarenco P, Lamonte M, Gilbert S, Messig M, Callahan A, et al. Relative effects of statin therapy on stroke and cardiovascular events in men and women: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Study. Stroke; a journal of cerebral circulation. 2008;39(9):2444-8.
248. Wang X, Dong Y, Qi X, Huang C, Hou L. Cholesterol levels and risk of hemorrhagic stroke: a systematic review and meta-analysis. Stroke; a journal of cerebral circulation. 2013;44(7):1833-9.
249. van Swieten JC, Hijdra A, Koudstaal PJ, van Gijn J. Grading white matter lesions on CT and MRI: a simple scale. Journal of neurology, neurosurgery, and psychiatry. 1990;53(12):1080-3.
250. Charidimou A, Schmitt A, Wilson D, Yakushiji Y, Gregoire SM, Fox Z, et al. The Cerebral Haemorrhage Anatomical RaTing inStrument (CHARTS): Development and assessment of reliability. Journal of the neurological sciences. 2017;372:178-83.
251. Zia E, Engstrom G, Svensson PJ, Norrving B, Pessah-Rasmussen H. Three-year survival and stroke recurrence rates in patients with primary intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2009;40(11):3567-73.
252. Hill MD, Silver FL, Austin PC, Tu JV. Rate of stroke recurrence in patients with primary intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2000;31(1):123-7.
253. Passero S, Burgalassi L, D'Andrea P, Battistini N. Recurrence of bleeding in patients with primary intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 1995;26(7):1189-92.
254. Bronnum Nielsen P, Larsen TB, Gorst-Rasmussen A, Skjoth F, Rasmussen LH, Lip GY. Intracranial hemorrhage and subsequent ischemic stroke in patients with atrial fibrillation: a nationwide cohort study. Chest. 2015;147(6):1651-8.
255. Chao TF, Liu CJ, Liao JN, Wang KL, Lin YJ, Chang SL, et al. Use of Oral Anticoagulants for Stroke Prevention in Patients With Atrial Fibrillation Who Have a History of Intracranial Hemorrhage. Circulation. 2016;133(16):1540-7.
256. Goldstein LB, Amarenco P, Szarek M, Callahan A, 3rd, Hennerici M, Sillesen H, et al. Hemorrhagic stroke in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels study. Neurology. 2008;70(24 Pt 2):2364-70.

257. FitzMaurice E, Wendell L, Snider R, Schwab K, Chanderraj R, Kinnecom C, et al. Effect of statins on intracerebral hemorrhage outcome and recurrence. Stroke; a journal of cerebral circulation. 2008;39(7):2151-4.
258. Schmidt LB, Goertz S, Wohlfahrt J, Melbye M, Munch TN. Recurrent Intracerebral Hemorrhage: Associations with Comorbidities and Medicine with Antithrombotic Effects. PloS one. 2016;11(11):e0166223.
259. Chen PS, Cheng CL, Chang YC, Kao Yang YH, Yeh PS, Li YH. Early statin therapy in patients with acute intracerebral hemorrhage without prior statin use. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2015;22(5):773-80.
260. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137(2):263-72.
261. van den Ham HA, Klungel OH, Singer DE, Leufkens HG, van Staa TP. Comparative Performance of ATRIA, CHADS2, and CHA2DS2-VASc Risk Scores Predicting Stroke in Patients With Atrial Fibrillation: Results From a National Primary Care Database. Journal of the American College of Cardiology. 2015;66(17):1851-9.
262. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). European heart journal. 2016.
263. Okumura K, Inoue H, Atarashi H, Yamashita T, Tomita H, Origasa H, et al. Validation of CHA(2)DS(2)-VASc and HAS-BLED scores in Japanese patients with nonvalvular atrial fibrillation: an analysis of the J-RHYTHM Registry. Circulation journal : official journal of the Japanese Circulation Society. 2014;78(7):1593-9.
264. Lip GY, Frison L, Halperin JL, Lane DA. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. Stroke; a journal of cerebral circulation. 2010;41(12):2731-8.
265. Giralt-Steinhauer E, Cuadrado-Godia E, Ois A, Jimenez-Conde J, Rodriguez-Campello A, Soriano C, et al. Comparison between CHADS2 and CHA2 DS2 -VASc score in a stroke cohort with atrial fibrillation. European journal of neurology : the official journal of the European Federation of Neurological Societies. 2013;20(4):623-8.
266. Chao TF, Liu CJ, Wang KL, Lin YJ, Chang SL, Lo LW, et al. Incidence and prediction of ischemic stroke among atrial fibrillation patients with end-stage renal disease requiring dialysis. Heart rhythm : the official journal of the Heart Rhythm Society. 2014;11(10):1752-9.
267. Lau KK, Chan PH, Yiu KH, Chan YH, Liu S, Chan KH, et al. Roles of the CHADS2 and CHA2DS2-VASc scores in post-myocardial infarction patients: Risk of new occurrence of atrial fibrillation and ischemic stroke. Cardiol J. 2014;21(5):474-83.
268. Xiong Q, Chen S, Senoo K, Proietti M, Hong K, Lip GY. The CHADS2 and CHA2DS2-VASc scores for predicting ischemic stroke among East Asian patients with atrial fibrillation: A systemic review and meta-analysis. Int J Cardiol. 2015;195:237-42.
269. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA : the journal of the American Medical Association. 1994;271(11):840-4.
270. Walsh KB, Woo D, Sekar P, Osborne J, Moomaw CJ, Langefeld CD, et al. Untreated Hypertension: A Powerful Risk Factor for Lobar and Nonlobar Intracerebral Hemorrhage in Whites, Blacks, and Hispanics. Circulation. 2016;134(19):1444-52.

271. O'Donnell MJ, Chin SL, Rangarajan S, Xavier D, Liu L, Zhang H, et al. Global and regional effects of potentially modifiable risk factors associated with acute stroke in 32 countries (INTERSTROKE): a case-control study. Lancet. 2016;388(10046):761-75.
272. Hankey GJ, Stevens SR, Piccini JP, Lokhnygina Y, Mahaffey KW, Halperin JL, et al. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. Stroke; a journal of cerebral circulation. 2014;45(5):1304-12.
273. O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. European heart journal. 2015;36(46):3258-64.
274. Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, et al. Major bleeding and intracranial hemorrhage risk prediction in patients with atrial fibrillation: Attention to modifiable bleeding risk factors or use of a bleeding risk stratification score? A nationwide cohort study. Int J Cardiol. 2018;254:157-61.
275. Charidimou A, Martinez-Ramirez S, Shoamanesh A, Oliveira-Filho J, Frosch M, Vashkevich A, et al. Cerebral amyloid angiopathy with and without hemorrhage: evidence for different disease phenotypes. Neurology. 2015;84(12):1206-12.
276. Rodrigues MA, Samarasekera N, Lerpiniere C, Humphreys C, McCarron MO, White PM, et al. The Edinburgh CT and genetic diagnostic criteria for lobar intracerebral haemorrhage associated with cerebral amyloid angiopathy: model development and diagnostic test accuracy study. Lancet neurology. 2018;17(3):232-40.
277. Charidimou A, Jager RH, Peeters A, Vandermeeren Y, Laloux P, Baron JC, et al. White matter perivascular spaces are related to cortical superficial siderosis in cerebral amyloid angiopathy. Stroke; a journal of cerebral circulation. 2014;45(10):2930-5.
278. Charidimou A, Hong YT, Jager HR, Fox Z, Aigbirhio FI, Fryer TD, et al. White matter perivascular spaces on magnetic resonance imaging: marker of cerebrovascular amyloid burden? Stroke; a journal of cerebral circulation. 2015;46(6):1707-9.
279. Fotiadis P, van Rooden S, van der Grond J, Schultz A, Martinez-Ramirez S, Auriel E, et al. Cortical atrophy in patients with cerebral amyloid angiopathy: a case-control study. Lancet neurology. 2016;15(8):811-9.
280. Dumas A, Dierksen GA, Gurol ME, Halpin A, Martinez-Ramirez S, Schwab K, et al. Functional magnetic resonance imaging detection of vascular reactivity in cerebral amyloid angiopathy. Annals of neurology. 2012;72(1):76-81.
281. Peca S, McCreary CR, Donaldson E, Kumarpillai G, Shobha N, Sanchez K, et al. Neurovascular decoupling is associated with severity of cerebral amyloid angiopathy. Neurology. 2013;81(19):1659-65.
282. Switzer AR, McCreary C, Batool S, Stafford RB, Frayne R, Goodyear BG, et al. Longitudinal decrease in blood oxygenation level dependent response in cerebral amyloid angiopathy. Neuroimage Clin. 2016;11:461-7.
283. Farid K, Hong YT, Aigbirhio FI, Fryer TD, Menon DK, Warburton EA, et al. Early-Phase 11C-PiB PET in Amyloid Angiopathy-Related Symptomatic Cerebral Hemorrhage: Potential Diagnostic Value? PloS one. 2015;10(10):e0139926.
284. Gurol ME, Becker JA, Fotiadis P, Riley G, Schwab K, Johnson KA, et al. Florbetapir-PET to diagnose cerebral amyloid angiopathy: A prospective study. Neurology. 2016;87(19):2043-9.
285. Lau KK, Lovelock CE, Li L, Simoni M, Gutnikov S, Kuker W, et al. Antiplatelet Treatment After Transient Ischemic Attack and Ischemic Stroke in Patients With Cerebral Microbleeds in 2 Large Cohorts and an Updated Systematic Review. Stroke; a journal of cerebral circulation. 2018;49(6):1434-42.

286. Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet. 2016.
287. Hilkens NA, van Asch CJJ, Werring DJ, Wilson D, Rinkel GJE, Algra A, et al. Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score. Journal of neurology, neurosurgery, and psychiatry. 2018.
288. Schulman S. Resumption of oral anticoagulation after warfarin-associated intracerebral hemorrhage: no. Stroke; a journal of cerebral circulation. 2011;42(12):3663-4.
289. Steiner T. Resumption of oral anticoagulation after warfarin-associated intracerebral hemorrhage: yes. Stroke; a journal of cerebral circulation. 2011;42(12):3661-2.
290. Pasquini M, Charidimou A, van Asch CJ, Baharoglu MI, Samarasekera N, Werring DJ, et al. Variation in restarting antithrombotic drugs at hospital discharge after intracerebral hemorrhage. Stroke; a journal of cerebral circulation. 2014;45(9):2643-8.
291. Murthy SB, Gupta A, Merkler AE, Navi BB, Mandava P, Iadecola C, et al. Restarting Anticoagulant Therapy After Intracranial Hemorrhage: A Systematic Review and Meta-Analysis. Stroke; a journal of cerebral circulation. 2017;48(6):1594-600.
292. Biffi A, Kuramatsu JB, Leasure A, Kamel H, Kourkoulis C, Schwab K, et al. Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage. Annals of neurology. 2017;82(5):755-65.
293. Kim BJ, Lee EJ, Kwon SU, Park JH, Kim YJ, Hong KS, et al. Prevention of cardiovascular events in Asian patients with ischaemic stroke at high risk of cerebral haemorrhage (PICASSO): a multicentre, randomised controlled trial. Lancet neurology. 2018;17(6):509-18.
294. Microbleeds International Collaborative N. Worldwide collaboration in the Microbleeds International Collaborative Network. Lancet neurology. 2016;15(11):1113-4.
295. Horstmann S, Zugck C, Krumsdorf U, Rizos T, Rauch G, Geis N, et al. Left atrial appendage occlusion in atrial fibrillation after intracranial hemorrhage. Neurology. 2014;82(2):135-8.
296. Qureshi AI, Tuhrim S, Broderick JP, Batjer HH, Hondo H, Hanley DF. Spontaneous intracerebral hemorrhage. The New England journal of medicine. 2001;344(19):1450-60.
297. Kitamura A, Nakagawa Y, Sato M, Iso H, Sato S, Imano H, et al. Proportions of stroke subtypes among men and women > or =40 years of age in an urban Japanese city in 1992, 1997, and 2002. Stroke; a journal of cerebral circulation. 2006;37(6):1374-8.
298. Biomarkers Definitions Working G. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3):89-95.
299. Hijazi Z, Oldgren J, Lindback J, Alexander JH, Connolly SJ, Eikelboom JW, et al. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. Lancet. 2016;387(10035):2302-11.
300. Yamamoto N, Satomi J, Yamamoto Y, Izumi Y, Nagahiro S, Kaji R. Usefulness of 3-Tesla magnetic resonance arterial spin-labeled imaging for diagnosis of cranial dural arteriovenous fistula. Journal of the neurological sciences. 2017;372:428-32.
301. Griffanti L, Zamboni G, Khan A, Li L, Bonifacio G, Sundaresan V, et al. BIANCA (Brain Intensity AbNormality Classification Algorithm): A new tool for automated segmentation of white matter hyperintensities. Neuroimage. 2016;141:191-205.
302. Rincon M, Diaz-Lopez E, Selnes P, Vegge K, Altmann M, Fladby T, et al. Improved Automatic Segmentation of White Matter Hyperintensities in MRI Based on Multilevel Lesion Features. Neuroinformatics. 2017;15(3):231-45.
303. Zou X, Hart BL, Mabray M, Bartlett MR, Bian W, Nelson J, et al. Automated algorithm for counting microbleeds in patients with familial cerebral cavernous malformations. Neuroradiology. 2017;59(7):685-90.

304. Fazlollahi A, Meriaudeau F, Giancardo L, Villemagne VL, Rowe CC, Yates P, et al. Computer-aided detection of cerebral microbleeds in susceptibility-weighted imaging. Comput Med Imaging Graph. 2015;46 Pt 3:269-76.
305. Wu TY, Sobowale O, Hurford R, Sharma G, Christensen S, Yassi N, et al. Software output from semi-automated planimetry can underestimate intracerebral haemorrhage and peri-haematomal oedema volumes by up to 41. Neuroradiology. 2016;58(9):867-76.
306. Muschelli J, Sweeney EM, Ullman NL, Vespa P, Hanley DF, Crainiceanu CM. PItcHPERFeCT: Primary Intracranial Hemorrhage Probability Estimation using Random Forests on CT. Neuroimage Clin. 2017;14:379-90.
307. Madai VI, von Samson-Himmelstjerna FC, Bauer M, Stengl KL, Mutke MA, Tovar-Martinez E, et al. Ultrahigh-field MRI in human ischemic stroke--a 7 tesla study. PloS one. 2012;7(5):e37631.
308. Theysohn JM, Kraff O, Maderwald S, Barth M, Ladd SC, Forsting M, et al. 7 tesla MRI of microbleeds and white matter lesions as seen in vascular dementia. J Magn Reson Imaging. 2011;33(4):782-91.
309. Bian W, Hess CP, Chang SM, Nelson SJ, Lupo JM. Susceptibility-weighted MR imaging of radiation therapy-induced cerebral microbleeds in patients with glioma: a comparison between 3T and 7T. Neuroradiology. 2014;56(2):91-6.
310. Kang CK, Worz S, Liao W, Park CA, Kim YB, Park CW, et al. Three dimensional model-based analysis of the lenticulostriate arteries and identification of the vessels correlated to the infarct area: preliminary results. International journal of stroke : official journal of the International Stroke Society. 2012;7(7):558-63.
311. Vogenberg FR, Isaacson Barash C, Pursel M. Personalized medicine: part 1: evolution and development into theranostics. P T. 2010;35(10):560-76.