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NARRATIVE REVIEW

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Secondary prevention after intracerebral haemorrhage

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Abstract

Background: Intracerebral haemorrhage (ICH) has high mortality in the acute phase and poor functional outcome in the majority of survivors. ICH recurrence is a major determinant of long-term prognosis and is the most feared complication of antithrombotic treatment. On the other hand, ICH patients are at high risk of future ischaemic vascular events.

Methods: This narrative review provides a critical analysis of the current knowledge on the topic. We performed a Pubmed search with the following terms 'intracerebral haemorrhage', 'stroke', 'outcome', 'secondary prevention', 'anticoagulation' and 'atrial fibrillation', including only English written studies with no time restrictions.

Results: Blood pressure management is the cornerstone of secondary ICH prevention, regardless of ICH location or underlying cerebral small vessel disease. Resumption of antiplatelet and anticoagulation therapy is often challenging, with limited evidence from randomized trials. Clinical and imaging predictors can inform the stratification of ICH recurrence risk and might identify patients at very high probability of future haemorrhagic events. This narrative review provides a summary of the main diagnostic tools and therapeutic strategies available for secondary prevention in ICH survivors.

Conclusion: Appropriate recognition and treatment of modifiable risk factors for ICH recurrence might improve outcomes in ICH survivors. Ongoing randomized trials might provide novel insights and improve long-term management.

KEYWORDS

anticoagulation, atrial fibrillation, intracerebral haemorrhage, outcome, secondary prevention, stroke

1 | INTRODUCTION

Spontaneous Intracerebral Haemorrhage (ICH) is the second cause of cerebrovascular accidents (CVA) worldwide and a significant determinant of disability and mortality.[1,2] ICH recurrence is not uncommon and the long-term rate of recurrent ICH for early survivors ranges from 1.3% to 7.4% per year, with the higher event rate in the first year after the index haemorrhage.[3] In addition, ICH survivors are at high risk of major ischaemic events,

such as ischaemic stroke or myocardial infarction, mainly because of their vascular risk factor profile.[4] Recurrent ICH accounts for 14% of deaths in ICH patients surviving the acute phase, while ischaemic stroke accounts for 5% of long-term deaths.[5] Several ICH survivors have strong indications for introduction or resumption of antithrombotic therapies after the acute event. On the other hand, antithrombotic treatment might increase the risk of ICH recurrence and management of such therapies is often challenging in clinical practice.[6] Clinical and radiological factors can guide clinicians and help the stratification of ICH recurrence and ischaemic events risk. In this review, we provide a summary of ischaemic and haemorrhagic risk stratification in ICH survivors and discuss long-term therapeutic strategies.

2 | STRATIFICATION OF ISCHAEMIC AND HAEMORRHAGIC RISK

The risk of major ischaemic events can be estimated with the CHA_2DS_2-VASc score, a validated tool with good predictive performance. Predictive major bleeding scores such as the HASBLED and ATRIA showed poor predictive value, and moreover do not discriminate between intra or extracranial haemorrhages, with the former having significantly higher mortality. A new imaging-based risk score for the prediction of ICH and ischaemic stroke in patient taking antithrombotic therapy has been recently developed. This Microbleeds International Collaborative Network (MICON) risk score for ICH includes clinical variables and MRI-detected cerebral microbleeds and showed a good predictive performance. However, it has not been externally validated and it remains unclear whether it can accurately identify patients more likely to benefit from specific therapies.[7]

2.1 | Risk of ischaemic vascular events

ICH survivors face a heightened risk of ischaemic events. These events are not uncommon, and they have been estimated around 1% to 6% for ischaemic stroke and up to 4% for myocardial infarction.[8] Li and Murthy have recently reviewed population- and in-hospital-based studies enrolling more than 26,000 ICH survivors worldwide from 1978 up to the present. The median rate of recurrent ischaemic stroke was about 5% with an annual rate of 2% over 3 years of median follow-up.[8] The most recent analyses focused on timing of ischaemic events and confirmed a high cumulative rate at 1 year that significantly increase with age.[9,10] The risk of ischaemic events remains consistently elevated even long-term reaching 10-year rates of 40% in the elderly.[9,10]

The site of index ICH could further confer a different risk of ischaemic events as this seems greater in deep rather than in lobar ICH, but recent evidence yielded conflicting results.[4,11,12] The risk of ischaemic events after a prior ICH is influenced by the presence of vascular risk factors, atherothrombotic disease and even more, atrial fibrillation (AF) that confers an ischaemic risk higher than that expected based on the CHA_2DS_2-VASc score alone.[13,14] Concomitant AF indeed doubles ischaemic stroke risk in these patients as compared with general population. Such risk seems higher in the first year and is due to the disease itself as well as to the discontinuation of antithrombotic therapy after index ICH.[15,16]

2.2 | Risk of ICH recurrence

2.2.1 | Clinical predictors

The clinical history of ICH survivors is traditionally challenged by risk of recurrence. Many of the risk factors leading to the index ICH indeed persist and increase the risk of recurrent events.[17] Age, Asian or Black race and presence of the APOE ε2 or ε4 alleles are the main non-modifiable risk factors increasing the odds of recurrent ICH. Conversely, elevated blood pressure is the main modifiable determinant of ICH recurrence and the most appealing therapeutic target.[18,19] APOE ε2 or ε4 alleles both increase the risk of recurrent symptomatic lobar ICH. Moreover, APOE ε4 is also associated with increased risk of non-lobar ICH and this association might be modulated by LDL cholesterol levels.[18] Inadequate blood pressure (BP) control is associated with a higher risk of ICH recurrence regardless of the index ICH location. The recurrence risk linked to hypertension is higher in the first 3 months after the first event.[20] Biffi et al. demonstrated an increased risk of recurrent ICH for all hypertension stages above normotension (defined as systolic blood pressure (SBP) of 90–119 mm Hg and diastolic blood pressure (DBP) of 60–79 mm Hg) and showed a continuous correlation between SBP values and ICH recurrence risk for both lobar and non-lobar ICH survivors. ICH recurrence risk seems unaffected by the type or number of antihypertensive medications used.[19]

2.2.2 | Imaging predictors

As anticipated, index ICH location is important when stratifying the risk of recurrency. Patients with prior lobar ICH have a higher risk of recurrence. A prospective

observational cohort study showed a cumulative incidence rate of recurrence of 6.1% in the first year and 7.9% at 5 years after a lobar ICH, while the cumulative incidence rate was lower (2.6% at 1 year and 3.2% at 5 years) after non-lobar disease.[4] Furthermore, the evidence of cerebral amyloid angiopathy (CAA) is associated with a higher risk of recurrent events.[3] In patients with lobar ICH due to CAA, the presence of disseminated cortical superficial siderosis (cSS) or acute convexity subarachnoid haemorrhage (cSAH) further increases the risk of early ICH recurrence.[21,22] cSS is due to the deposition of blood-breakdown product limited to cortical sulci over the convexities of the cerebral hemispheres and represents an MRI marker of recurrence, visible with T2-gradient recalled echo (T2-GRE) or other susceptibility-weighted sequences. cSAH predicts the risk of recurrent ICH (HR 2.53, 95% CI 1.39–4.62; $p = 0.002$) and can be used as a non-contrast-computed tomography (NCCT) marker of ICH recurrence when magnetic resonance imaging (MRI) is not available or contraindicated.[21,22] A previous meta-analysis found significantly elevated risk for recurrent ICH in patients with CMBs, independently of CAA. In particular, for CAA-unrelated ICH more than 10 CMBs predicted high recurrent ICH risk. No relationship was found in the presence of a single CMB compared to CMBs absence. When CMBs and cSS were analysed together in the same predictive model, the association between CMBs and ICH recurrence was no longer significant whereas cSS remained the strongest predictor of future ICH in ICH survivors.[23] Figures 1 and 2 provide illustrative examples of NCCT and MRI markers of ICH recurrence.

3 | BLOOD PRESSURE LOWERING

In patients with spontaneous ICH, BP control is recommended to prevent haemorrhage recurrence. BP-lowering also reduces the risk of ischaemic events and might mitigate the progression of cerebral small vessel disease which contributes to the delayed cognitive impairment and dementia that follow ICH.[24] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) study and subsequent post-hoc analyses showed that patients with the lowest BP levels during follow-up had the lowest risk of stroke recurrence, both ischaemic and haemorrhagic ones. Strong relationship was found between lower SBP levels and haemorrhagic stroke (P homogeneity = 0.003) with a relative risk reduction of 49% (95% CI, 18%–68%). Among ICH patients, BP lowering reduces the risk of all type of haemorrhage, both hypertension- and CAA-related.[25–27] Yet, the benefit of intensive vs standard BP lowering for the prevention of recurrent cerebral infarction is less clear. The RESPECT Study showed that lowering BP to a target goal less than 120/80 mm Hg compared with the standard goal of 140/90 mm Hg resulted in non-significant reductions of all strokes.[28] On the other hand, a recent study showed an association between intensive SBP reduction with a decreased risk for recurrent ICH and major adverse cardiovascular and cerebrovascular events without increasing all-cause mortality and vascular mortality. However, among patients aged >75 years and with greater post-ICH disability (modified Rankin Scale score of 4 to 5 at discharge), SBP < 120 mm Hg was associated with increased all-cause mortality but not vascular mortality.[29] Despite antihypertensive therapy, BP control is often found inadequate at follow-up. Studies showed that a minority of survivors achieved adequate BP control, with suboptimal BP control in more than 50% of ICH survivors.[19,20] Poor BP control might be explained by undertreatment -especially in lobar ICH survivors- or by resistant hypertension more often found in Black, Hispanic and Asian people.[20,30] There is limited evidence about the optimal antihypertensive drugs to use after ICH events. Guidelines for management of hypertension suggest as

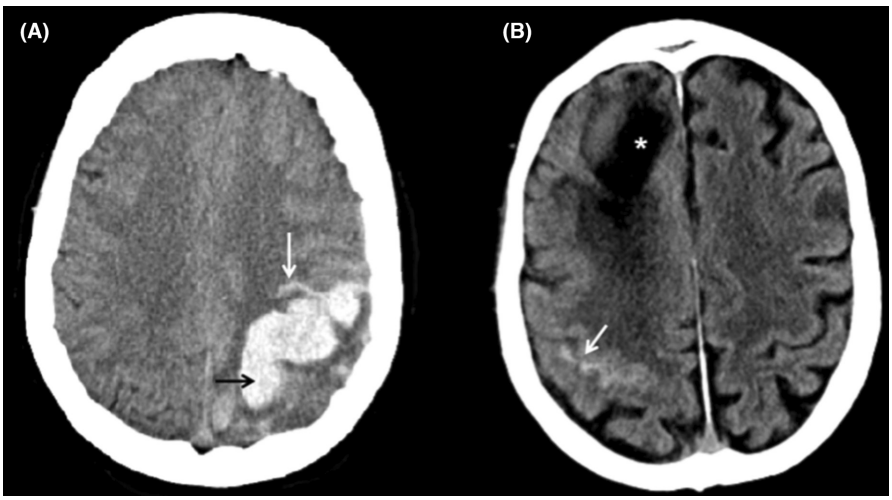

FIGURE 1 NCCT markers of ICH recurrence. (A) Lobar ICH with subarachnoid extension (white arrow) and «finger-like» projection (black arrow). (B) Acute cSAH (arrow) in a patient with CAA and previous lobar ICH (asterisk). Abbreviations: CAA, cerebral amyloid angiopathy; cSAH, convexity subarachnoid haemorrhage; ICH, intracerebral haemorrhage, NCCT, non-contrast computed tomography.

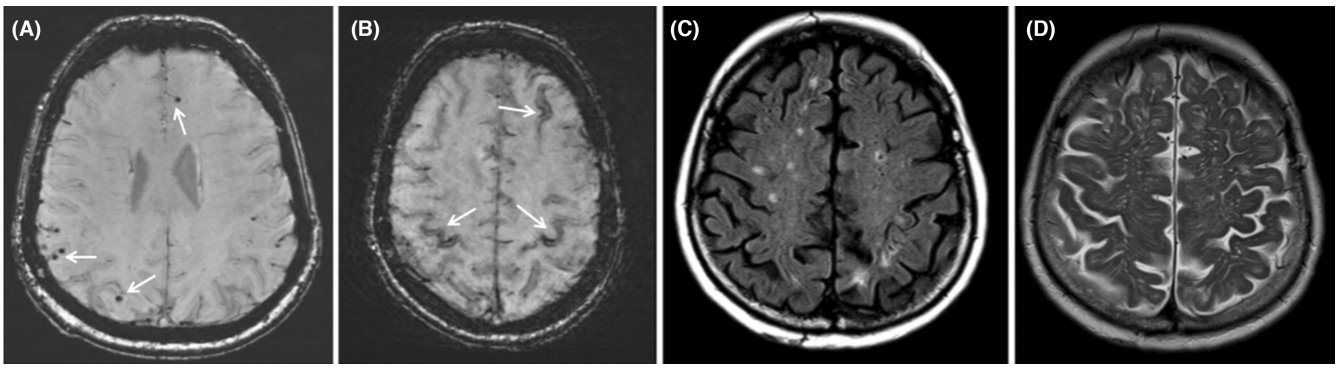

FIGURE 2 MRI markers of ICH recurrence. (A) Multiple lobar microbleeds. (B) Multifocal cortical superficial siderosis. (C) White matter hyperintensities with a «spot-like» pattern. (D) Enlarged perivascular spaces in the centrum semiovalis. Abbreviations: ICH, intracerebral haemorrhage, MRI, magnetic resonance imaging.

first line the use of renin-angiotensin-system blockers, calcium channel blockers or a thiazide-like diuretic or a combination of these therapies as secondary prevention in patients with previous stroke or cerebrovascular disease.[31,32] Regarding haemorrhagic events, the PROGRESS study showed greater benefits with a combination therapy based on an angiotensin-converting enzyme inhibitor and a diuretic compared with placebo or single-drug therapy in all types of ICH.[25–27] Guidelines recommend lowering SBP below 130 mm Hg and DBP below 80 mm Hg.[33] BP levels should be assessed regularly in all patients regardless of age, location or presumed small vessel disease underlying the acute ICH.[24,26]

4 | ANTITHROMBOTIC TREATMENT

4.1 | Antiplatelet resumption

Solid evidence suggests that antiplatelet resumption is safe in the majority of patients with ICH.[34,35] The RESTART trial (Restart or Stop Antithrombotics Randomized Trial) is the only randomized controlled trial that compared the effects of starting or avoiding antiplatelet therapy after ICH. Recent findings after extended follow-up (max 7 years) showed a similar risk of recurrent ICH in patients restarting or avoiding antiplatelet therapy (8.2% and 9.3% recurrence rate respectively, HR, 0.87; 95% CI, 0.49–1.55). No statistically significant reduction of all major vascular event was found between the two groups.[35,36] In line with the AHA/ASA guidelines, we suggest antiplatelet resumption for most patients with a strong indication such as established atherosclerotic disease and/or secondary prevention of ischaemic stroke or myocardial infarction. On the opposite, very limited evidence is available about the optimal timing of resumption. Likewise, it remains unclear whether there is an interaction between ICH location, small vessel disease burden and safety of antiplatelet therapy in ICH survivors. The risk/benefit ratio of antiplatelets might be less favourable in selected patients with lobar ICH due to CAA and very high risk of ICH recurrence.[37]

4.2 | Anticoagulant resumption

In patient at very high thromboembolic risk (presence of ventricular assist device (LVAD), presence of mechanical heart valve (MHV)), resumption of anticoagulant therapy after spontaneous ICH is reasonable after 2 weeks from the ICH event.[6,33] Different studies showed that earlier resumption of anticoagulation was associated with increased haemorrhagic complications.[38–40] Resumption at day six from the index ICH might be considered only in patient with MHV and presumed to be at very high risk of thromboembolic events.[38] In patients with non-valvular AF oral anticoagulant therapy (OAT) resumption seemed associated with a decreased risk of thromboembolic events without significant increase in the risk of major bleeding.[41–43] Until 2015 international guidelines gave different indication for lobar and non-lobar ICH survivors.[44] Recent evidence suggests that anticoagulation, when indicated, might be considered regardless of ICH location.[41,42] Biffi et al. in a meta-analysis of three observational studies showed that OAT resumption in both lobar and non-lobar ICH survivors resulted in decreased all-stroke and ischaemic stroke incidence at 1 year. OAT resumption was significantly associated with decreased mortality and favourable functional outcome both in lobar and non-lobar ICH. In line with previous literature, recurrent ICH, haemorrhagic risk was higher in lobar than non-lobar haemorrhages, but OAT resumption was associated with better outcome also in patients with CAA-related lobar ICH.[41] The optimal time to restart anticoagulation therapy seems to be at around 7–8 weeks after the

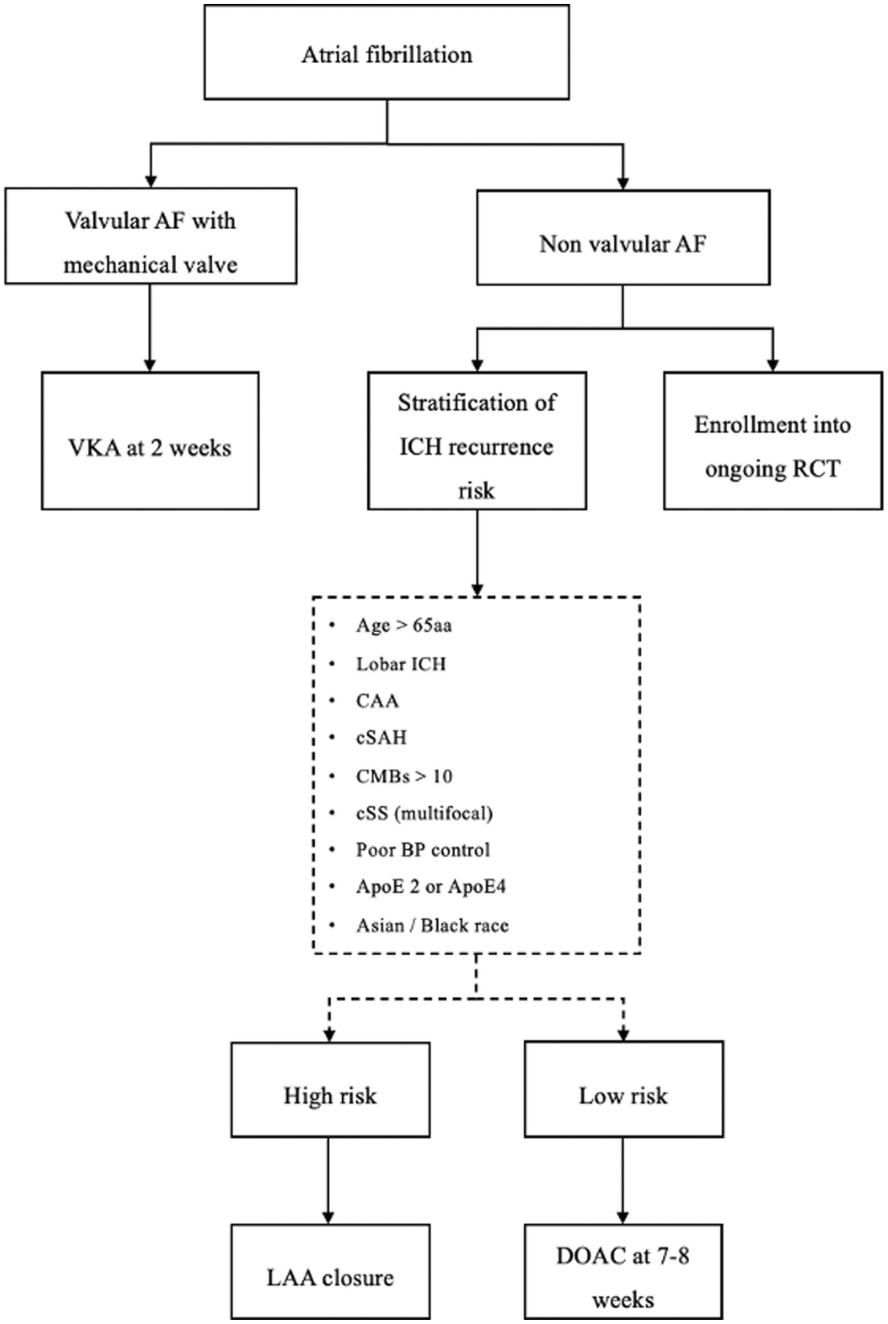

FIGURE 3 Atrial fibrillation management after ICH. Abbreviations: AF, atrial fibrillation; BP, blood pressure; CAA, cerebral amyloid angiopathy, CMBs, cerebral microbleeds; cSAH, convexity subarachnoid haemorrhage; cSS, cortical superficial siderosis; DOAC, direct oral anticoagulants; ICH, intracerebral haemorrhage; LAA, Left Atrial Appendage; RCT, randomized controlled trial, VKA, vitamin K antagonist.

bleeding event,[43] however the evidence remains limited. Notably, the currently available and above-mentioned evidence on OAT resumption in ICH survivors is influenced by confounding by indication bias and results from randomized trials are still inconclusive.[45] Two prospective randomized clinical trials investigated the safety and efficacy of OAT. The SoSTART trial did not demonstrate non-inferiority of OAT compared to avoiding oral anticoagulation. In the restart arm, recurrent symptomatic spontaneous intracranial haemorrhages were more frequent and often fatal.[46] The APACHE-AF trial found no differences between restarting Apixaban and avoiding anticoagulation for the prevention of non-fatal stroke or vascular death.[47] Direct oral anticoagulants (DOACs) represent an appealing therapeutic strategy, because of their lower risk of intracranial bleeding compared to vitamin K antagonists (VKA).[48] Resumption of anticoagulant therapy in clinical practice is based on individual assessment of the balance between thromboembolic risk and the odds of recurrent ICH.[33,49] Although there is limited evidence on the use of DOACs in ICH survivors, these should be considered the first choice in patients with non-valvular AF because of their favourable risk profile and lower ICH risk compared to VKA.[50,51] Clinical, epidemiological and imaging characteristics might help the risk/benefit estimation of OAT resumption and a practical flowchart for AF management in ICH survivors is provided in Figure 3.

4.3 | Left atrial appendage closure

Left Atrial Appendage (LAA) closure procedure is based on the fact that during AF, the LAA is the place where most thrombi form LAA closure has the final goal of excluding this anatomical part from the circulation preventing both thrombus formation and embolization trough (1) LAA neck obstruction by endovascular delivery of a device lobe or umbrella; (2) endovascular introduction of a device within the LAA including a disk sealing the ostium; (3) surgical LAA occlusion (e.g. LAA neck loop ligation), excision or resection.[52,53] Available evidence on LAA closure safety and efficacy vs. OAT relies on very few clinical trials and many more observational registries, therefore recommendations for LAA closure in current guidelines remain weak and based on a poor evidence level.[54] ESC guidelines for AF management 2020 recommend to consider (class IIb, level of evidence B) LAA occlusion for stroke prevention in patients with AF and contraindications to long-term anticoagulant treatment.[55] Furthermore, clinicians should take into account that most centres suggest dual or single antiplatelet therapy for variable time (3–6 months) after occluding device implantation; LAA neck ligation or thoracospic LAA clipping may be an alternative approach for those patients not even tolerating short-term antiplatelet therapy.[54] Other clinical scenarios in which LAA closure may be considered as suggested by an European expert consensus include (1) patients with an elevated bleeding risk during long-term OAT (HAS-BLED ≥3, tumour, thrombocytopenia, need for long-term or repetitive triple therapy, severe renal failure contraindicating DOAC); (2) AF patients unable or unwilling to take OAT after personal and detailed discussion and previous attempts to resolve any reasons for non-compliance (LAA occlusion should not be offered as a simple and equally effective alternative to OAT).[54] With specific reference to secondary prevention after ICH, patients with AF and prior ICH are often at high risk of recurrent life-threatening or disabling bleeding and therefore not prescribed with OAT and left unprotected against ischaemic stroke. LAA closure represents an attractive solution for this group of patients, despite the need of short OAT or dual antiplatelet therapy after implantation. A propensity score-matched follow-up study from 2017 enrolling 151 patients with previous LAA closure suggested LAA closure to be of major clinical benefit in AF patients with prior ICH.[56] A recent systematic review evaluating the outcomes of LAA closure in AF patients with prior ICH and AF included 7 studies and a total of 407 patients concluding that LAA closure is a safe and effective therapeutic option in such patients with acceptable periprocedural and post-procedure risks.[57] The ongoing "Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Hemorrhage" (STROKE-CLOSE) trial is expected to produce high-quality evidence for this specific subgroup of AF patients (clinicaltrials.gov, NCT02830152).

5 | LIPID-LOWERING MEDICATIONS

5.1 | Statins

Statins might increase the risk of ICH through several mechanisms, including reduced clot formation, inhibition of platelet activity, fibrinolysis enhancement and reduction of LDL cholesterol.[58] Several studies, including secondary analyses of the SPARCL trial, showed an increased incidence of haemorrhagic stroke in statin users after ischaemic-stroke patients[59–61] and suggested that LDL levels reduction below 70 mg/mL as the biological mediator of such association.[62] The influence of statin type and treatment intensity remains controversial. Some studies showed a direct association between statin intensity and bleeding risk while others did not confirm this finding.[60,63] Hydrophilic statins might have a lower risk of ICH because of reduced brain penetration compared to lipophilic statins.[63] The decision to use statins in clinical practice relies on the balance between the known benefits of statins for primary and secondary prevention of ischaemic events and their potential for increased risk of ICH.[33] Guidelines and expert opinions suggest the maintenance of statins in patients with a strong indication such as atherothrombotic disease, myocardial infarction and ischaemic stroke. Conversely, the risk/benefit ratio of statins might be less favourable in patients with weak indications and recurrent haemorrhagic events with underlying CAA. In patients at very high risk of ICH non-statin lipid-lowering treatment with ezetimibe and PCSK9 inhibitors might be considered.

5.2 | PCSK9 inhibitors

PCSK9 inhibitors are nowadays deemed as cornerstone therapies for cardiovascular (CV) and cerebrovascular disease prevention. Clinically approved PCSK9 inhibitors include inhibitory antibodies (i.e. alirocumab and evolocumab) as well as small interfering RNA (inclisiran). By reducing LDL receptor degradation, such drugs increase hepatic LDL uptake thereby reducing circulating lipoprotein levels to an extent unachievable by statin therapy.[64] Use of PCSK9 inhibitors in combination or not with statin and ezetimibe is likely going to increase by far in the coming years as an effect of the more stringent cholesterol

TABLE 1 Main ongoing randomized clinical trials in ICH survivors.

Study name	Population	Intervention	Comparator	Primary outcome
TRIDENT The Triple Therapy Prevention of Recurrent Intracerebral Disease Events Trial; NCT02699645	Adults ≥18 years, primary ICH and SBP in the range of 130–160 mm Hg	Telmisartan 20 mg, Amlodipine 2.5 mg, and Indapamide 1.25 mg	Placebo	Time to first recurrent stroke (ischaemic or haemorrhagic)
PROHIBIT-ICH Prevention of Hypertensive Injury to the Brain by Intensive Treatment in Intra-Cerebral Haemorrhage; NCT03863665	Adults ≥40 years with spontaneous primary ICH, SBP ≥130 mm Hg	Telemetric Bluetooth home BP monitors	Standard clinical care	Significant SBP reduction at 3 months
REDUCE Regulating Blood Pressure During Recovery From Intracerebral Haemorrhage, NCT04760717	Age ≥18 years, ICH, eGFR >45 mL/min, SBP 120–200 mm Hg	Spironolactone in addition to normal routine blood pressure treatment	Standard of Care	Average change in home SBP at 3 months
A3ICH Avoiding Anticoagulation After IntraCerebralHaemorrhage, NCT03243175	Age ≥18 years history of paroxysmal, persistent or long-standing non-valvular AF with indication for long-term anticoagulation	Apixaban 5 mg twice daily or LAA closure	No Intervention	Composite of all fatal or non-fatal major cardiovascular/cerebrovascular ischaemic or haemorrhagic events
ASPIRE Anticoagulation in ICH Survivors for Stroke Prevention and Recovery, NCT03907046	Age ≥18 years non-valvular AF, CHA2DS2-VASc score ≥2	Apixaban 5 mg twice daily or Apixaban 2.5 mg twice daily if: (1) ≥2 of age ≥80 years, body weight ≤60 kg, or serum creatinine 1.5–2.4 mg/dL is present or (2) Patient is taking a strong CYP3A4/pGP inhibitor	Aspirin 81 mg once daily	Incidence of any stroke or death from any cause
ENRICH-AF EdoxabaN foR IntraCranial Haemorrhage Survivors With Atrial Fibrillation, NCT03950076	Age ≥45 years, previous intracranial bleeding (symptomatic, spontaneous and non-traumatic intraparenchymal, intraventricular, and/or cSAH, and symptomatic spontaneous or non-penetrating traumatic subdural haemorrhage) on or off antithrombotic haemorrhages on or off antithrombotic therapy, documented AF, CHA2DS2-VASc score ≥2	Edoxaban 60 or 30 mg daily (lower dose depending on clinical criteria)	No antithrombotic therapy or antiplatelet monotherapy	Stroke (ischaemic, haemorrhagic or unspecified) or any major bleeding
PRESTIGE-AF PREvention of STroke in Intracerebral haemorrhaGE Survivors With Atrial Fibrillation, NCT03996772	Age ≥18 years, documented AF, CHA2DS2-VASc score ≥2 for male, and CHA2DS2-VASc score ≥3 for female patients	Dabigatran, Apixaban, Rivaroxaban or Edoxaban	No Anticoagulation	Time to the first incident ischaemic stroke event or time to the first recurrent intracerebral haemorrhage event

(Continues)

TABLE 1 (Continued)

Study name	Population	Intervention	Comparator	Primary outcome
STATICH Study of Antithrombotic Treatment After IntraCerebralHaemorrhage, NCT03186729	Age ≥18 years, spontaneous, primary ICH, 1–180 days	Antithrombotic treatment (antiplatelet or anticoagulant)	No antithrombotic treatment	Fatal or non-fatal symptomatic ICH
STROKE-CLOSE Prevention of Stroke by Left Atrial Appendage Closure in Atrial Fibrillation Patients After Intracerebral Haemorrhage, NCT02830152	Age >18 years, paroxysmal, persistent or long-standing non-valvular AF with CHA2DS2VASc score >2	LAA closure, with the AMPLATZER™ Amulet™ device	Medical therapy	Composite endpoint of stroke (ischaemic or haemorrhagic), systemic embolism, life-threatening or major bleeding and all-cause mortality
SATURN Statins in Intracerebral Haemorrhage, NCT03936361	Age ≥50 years, spontaneous lobar ICH	Statin (the same statin agent and dose that subjects were using at the time of ICH onset)	No-statin (discontinuation of the statin agent taken at the time of ICH onset)	Recurrent symptomatic ICH

Abbreviations: AF, atrial fibrillation; BP, blood pressure; cSAH, convexity subarachnoid haemorrhage; eGFR, estimated glomerular filtration rate; ICH, intracerebral haemorrhage; LAA, left atrial appendage; SBP, systolic blood pressure.

targets suggested by guidelines in people at high- and very high-CV risk.[65,66] Those populations of course include individuals needing secondary prevention after a previous vascular event. It has been estimated that most recent ESC guidelines on dyslipidaemia management rendered half of all people in secondary CV prevention potentially eligible for receiving PCSK9 inhibition.[67] The protective cardio- and cerebrovascular effects of PCSK9 inhibitors have been attributed to a number of pleiotropic effects often independent of cholesterol levels.[68,69] While sharing anti-inflammatory and anti-oxidant effects, PCSK9 inhibitors seems to differ from statins on their effects on platelets aggregation and thrombogenicity at least in magnitude. Indeed, while experimental and clinical observations about their potential antiplatelet effects still report controversial results,[70,71] PCSK9 inhibitors had a very good safety profile, including haemorrhagic risk in all randomized clinical trials.[72–74] Such lower haemorrhagic propensity together with the greater lipid-lowering effects may suggest PCSK9 inhibitors as first choice rather than statins for patients at very high CV risk and at particular risk of bleedings, including those with prior ICH.[75]

6 | OTHER DRUGS

Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with an increased haemorrhagic risk. The mechanism of increased risk of bleeding is uncertain, but it might be related to platelet COX-1 activity inhibition. Increased haemorrhagic stroke risk was mainly observed with non-selective NSAIDs use, such as diclofenac and meloxicam, while selective COX-2 inhibitors showed safer bleeding risk profile.[76] Guidelines suggest to avoid daily use of NSAIDs in ICH survivors.[33] Selective serotonin reuptake inhibitors (SSRI) might also have an antithrombotic effect mediated by reduction of platelet aggregation and vasoconstriction.[77] SSRI exposure after ICH has been associated with an increased risk of recurrent haemorrhagic stroke[77] and should therefore be reserved to patients with a strong indication such as moderate to severe depression.[33]

7 | ONGOING TRIALS AND FUTURE PERSPECTIVES

Intensive BP lowering and antithrombotic drug management are the cornerstones of ICH secondary prevention and the focus of the majority of ongoing randomized trials, as summarized in Table 1. Stratification of ICH recurrence risk remains challenging in clinical practice. Advanced imaging with MRI might identify patients at

high risk of future ICH and therefore more likely to benefit from avoidance of long-term antithrombotic medications and intensive BP reduction.

8 | CONCLUSION

BP is the main modifiable risk factor for future ICH and a compelling target to improve patients' outcome. Ischaemic vascular events are a major determinant of morbidity and mortality in ICH survivors and many patients have strong indications for long-term antithrombotic treatment. Long-term antiplatelet and anticoagulant therapy management is based on the balance between thromboembolic risk and the probability of ICH recurrence. Imaging markers might improve the stratification of ICH risk and identify subjects at very high risk of rebleeding. The currently available evidence is biased by confounding by indication and ongoing randomized trials might provide novel insights and improve long-term management of ICH survivors.

AUTHOR CONTRIBUTIONS

All the other authors report no disclosures.

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CONFLICT OF INTEREST STATEMENT

LL is coinventor on the International Patent WO/2020/226993 filed in April 2020. The patent relates to the use of antibodies which specifically bind IL-1α to reduce various sequelae of ischaemia–reperfusion injury to the central nervous system. LL reports speaker fees outside of this work from Daichi-Sankyo.

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