ABSTRACT

Introduction: Spontaneous nontraumatic intracerebral hemorrhage (ICH) is most often caused by small vessel diseases: hypertensive arteriopathy or cerebral amyloid angiopathy (CAA). Although ICH accounts for only 10-15% of all strokes it causes a high proportion of stroke mortality and morbidity, with few proven effective acute or preventive treatments.

Areas covered: We conducted a literature search on etiology, diagnosis, treatment, management and current clinical trials in sICH. In this review we describe the causes, diagnosis, (including new brain imaging biomarkers), classification, pathophysiological understanding, treatment (medical and surgical) and secondary prevention of ICH.

Expert commentary: In recent years, significant advances have been made in deciphering causes, understanding pathophysiology, and improving acute treatment and prevention of ICH. However, the clinical outcome remains poor and many challenges remain. Acute interventions delivered rapidly (including medical therapies - targeting hematoma expansion, hemoglobin toxicity, inflammation, edema, anticoagulant reversal – and minimally-invasive surgery) are likely to improve acute outcomes. Improved classification of the underlying arteriopathy (from neuroimaging and genetic studies) and prognosis should allow tailored prevention strategies (including sustained blood pressure control and optimized antithrombotic therapy) to further improve longer-term outcome in this devastating disease.

1. Introduction

Non-traumatic intracerebral hemorrhage (ICH) is the most lethal form of stroke, with a mortality of over 50% at 1 year[1]. It accounts for 10-15% of all strokes in Western populations, and 18-20% in Asian populations[2-8]. Although ICH risk clearly increases with age, a substantial proportion occur in people under 50 years of age[9]. ICH causes a great burden for patients, carers, family members and society[10,11]. Unlike ischemic stroke the incidence of ICH is stable or increasing[5,12-15], probably in part explained by increased life expectancy and greater use of antithrombotic medications[12]. Unfortunately outcome after ICH has not improved over the last few decades[16]. Few evidence-based treatments have been available, leading to an attitude of clinical nihilism including early palliation[17]. However, in recent years, major new insights have emerged in the causes, diagnosis, classification, pathophysiological understanding, treatment and prevention of ICH, leading to growing research interest and a more pro-active approach, which we aim to summarize in this review.

2. Causes of ICH:

2.1. Small vessel disease and population risk factors

Non-traumatic ICH results from bleeding into the brain parenchyma arising from the rupture of an arterial vessel, most often (>80%) a small arteriole affected by cerebral small vessel diseases (SVD). Deep perforator arteriopathy (also termed hypertensive arteriopathy or arteriolosclerosis)[18,19] and cerebral amyloid angiopathy (CAA)[20,21] are the most common forms of sporadic SVD causing ICH. A minority of ICH (less than about 20%) is caused by macrovascular bleeding sources such as arteriovenous malformations, cavernomas or fistulas[22].

Deep perforator arteriopathy is linked with hypertension (though not exclusively) and is a frequent cause of non-lobar or deep ICH in the basal ganglia or brainstem, but also contributes to lobar hemorrhage [23]. CAA is caused by amyloid beta deposition in cortical and leptomeningeal blood vessels and is a major contributory cause of lobar ICH[19,24-26]. However, a recent post-mortem study[27] found that

36 of 62 patients (58%) with lobar ICH had moderate to severe CAA but only 10 of 62 patients (16%) had CAA alone. This, most older patients with lobar ICH are likely to have both CAA and other SVD including deep perforator arteriopathy. CAA also contributes substantially to cognitive impairment in the elderly population and is associated with Alzheimer's disease (AD)[19,28-31]. Based on MRI-findings, the modified Boston criteria (see Figure 1)[32] allow diagnosis of CAA in patients with ICH, providing different degrees of diagnostic certainty (possible, probable, or definite). The most useful category clinically is probable CAA defined as follows: age ≥55 years; multiple ICH (including CMBs) restricted to lobar, cortical or corticosubcortical regions on CT or MRI; or a single lobar, cortical or corticosubcortical ICH in addition to focal or disseminated superficial siderosis; and exclusion of other underlying cause of ICH. [32,33]; of note, the degree of investigation available could vary in different healthcare settings, which could affect diagnostic accuracy. Recently the Edinburgh criteria (see Figure 1)[34] have been developed, including acute CT and Apolipoprotein E genotype (APOE). The three component predictors for moderate or severe CAA are: subarachnoid extension; APOE ε4; and finger-like projections (elongated projections arising from the ICH, longer than they are wide, regardless of the direction of their extension, though without clear diagnostic criteria). An online training tool for the Edinburgh CT criteria is available (https://www.ed.ac.uk/clinical-sciences/edinburgh-imaging/education-teaching/short-courses/training-tools/edinburgh-criteria-for-caa-associated-ich-training). As the presence of APOE ε4 or subarachnoid hemorrhage had sensitivity of 100% for moderate or severe CAA, CAA-associated lobar ICH might be usefully ruled out in their absence[27]. On the other hand as the presence of APOE ε4 or subarachnoid hemorrhage and finger-like projections had a specificity of 96%, CAA-associated lobar ICH might be usefully ruled-in if these are present[27]. However, APOE4 is not routinely performed in most stroke units or reimbursed by medical insurance which limits the current applicability of this approach at a global level. In radiological-pathological validation studies both, the modified Boston and Edinburgh CT, criteria are reported to have excellent sensitivity and good specificity to diagnose CAA (Edinburgh CT criteria; Sensitivity: 100% 95%CI 88-100, Specificity: 96% 95%CI 78-100; modified Boston MRI criteria: Sensitivity: 94.7% 95%CI 82.8-98.5, Specificity: 81.2% 95%CI 61.5-92.7). Although the Edinburgh criteria were validated against the

gold standard – histopathology of the brain at autopsy – this validation study was prone to substantial selection bias as it included only patients with fatal IC; their diagnostic accuracy might be different in patients with less severe ICH. Furthermore, the Edinburgh criteria are only validated using acute CT scans so cannot be applied to patients beyond the acute phase of ICH. The Boston criteria have been validated using more limited tissue (e.g. biopsy, hematoma evacuation), which might be more representative of the whole ICH population (not only fatal or acute) but is more prone false-negative results for CAA pathology. Both the Boston or Edinburgh criteria have only been well validated in hospital ICH populations, and not general elderly or cognitively impaired populations.

A limitation of current diagnostic evaluation of ICH is that there are no validated imaging-based markers for deep perforator arteriopathy, and it is unknown whether there are further clinically important subgroups of ICH (i.e. mixed type or cryptogenic ICH [without visible signs of SVD]).

Nevertheless, attempts have been made for a clinical classification system of ICH subtypes (in analogy to existing systems for ischemic stroke: TOAST[35], ASCO[36,37] or CCS[38]). ICH can be either classified according to anatomy (i.e. lobar vs. non-lobar, supratentorial vs. infratentorial for example in the validated CHARTS scale[39], or to presumed mechanisms (i.e. etiology)[39,40]. “Mechanistic” classifications (H-ATOMIC[41] and SMASH-U[42] or from the Ludwigshafen Stroke Study[43]) include both actual bleeding sources (i.e. CAA and macrovascular lesions) and population “risk factors” (i.e. hypertension and use of antithrombotic medication) that probably mediate ICH risk by interactions with SVD. For example, although oral anticoagulation is a population risk factor for ICH[44], there is no evidence that these agents actually cause the rupture of cerebral arteries[45] It has been hypothesized that in the presence of oral anticoagulants, small cerebral microbleeds caused by SVD transform into clinically symptomatic ICH’s[45]. Nevertheless, ICH associated with oral anticoagulants accounts for approximately 15% of ICH[5,12-15].

Anatomical and mechanistic systems of classification both had excellent reliability when performed in experienced centers[40] but their performance outside specialist centers in unknown. Mechanistic

classification systems were mostly based on retrospective analysis and lack prospective evaluation for long-term prognosis and risk of recurrence.

The strongest population risk factors for ICH are hypertension, alcohol and psychosocial factors[46]; it is estimated that 82% of the attributable risk for ICH can be accounted for by known risk factors. In developed countries the incidence of ICH is not decreasing (by contrast with ischemic stroke), which might be due to the increased use of antithrombotic drugs (antiplatelet agents and anticoagulants) in older populations[14].

2.2. Genetics of ICH

The familial aggregation of ICH, as well as known heritable forms of CAA and ICH, support a genetic contribution to the ICH risk[47-50]. A population-based case–control study reported that having a first-degree relative with ICH increases the risk of ICH six-fold[6]. Indeed, the heritability of ICH has been estimated at 44%[51]. Both common and rare genetic variants could have a significant influence on the development as well as the functional outcome of ICH. Previous GWAS provide proof of concept that common variants are associated with both lobar as well as non-lobar ICH including Apolipoprotein E genotype (APOE) variants (rs7412 and rs429358), the rs4311 variant of the angiotensin-converting enzyme (ACE) gene and the rs9588151of the collagen type IV alpha 2 (COL4A2) gene [52-56]. APOE ε2 and ε4 are associated with lobar ICH; APOE ε4 might also be associated with non-CAA related, non-lobar ICH[52,57-59]. APOE ε2 might additionally have an influence on hematoma size, functional outcome and mortality, an important finding because ICH volume is an independent predictor of functional outcome and mortality [47,60]. A meta-analysis of data from the International Stroke Genetics Consortium (~1600 cases) also identified 1q22 as a susceptibility locus for non-lobar ICH, a locus potentially relevant to SVD[54]. A recent 2-stage case-only genome-wide association study of patients with ICH has identified a new risk locus, the 17p12 locus, to be associated with hemorrhage volume as well as functional outcome in non-lobar ICH[61]. Additionally, the CR1 variant rs6656401 influences CAA risk and the severity of amyloid deposition and can thereby influence ICH risk[62]. For further details of genetic influences on ICH please see a recent review[63]. Current international

collaborative efforts on large genome-wide association studies with enough power for genome-wide significance for new loci should help improve understanding disease pathways and developing new potential future therapeutic targets for ICH.

2.3. Diagnosis of ICH

Intracerebral hemorrhage is a life-threatening medical emergency that requires timely diagnosis; brain imaging is essential to reliably distinguish ICH from ischemic stroke so the emergency work-flow of patients with the suspicion of either ICH or ischemic stroke should be the same (i.e. focused neurological (GCS and NIHSS) and general medical assessments (airways, blood pressure, circulation) until a diagnosis has been established, usually with a CT scan which is highly sensitive for all forms of acute intracranial hemorrhage.

CT angiography or MR angiography are appropriate initial investigations to detect macrovascular bleeding sources. Initial diagnostic accuracy studies (comparing acute noninvasive angiography with the gold standard, digital subtraction angiography) suggested high specify and sensitivity[64]. However, more recent studies of sequential investigations suggest that diagnostic accuracy is modest when compared to the final diagnosis of a macrovascular cause after systematic investigation beyond the acute phase: for CTA sensitivity was 74% and specificity 91%[65].

Previous studies show great variability in the use of more invasive intra-arterial digital subtraction angiography (IADSA) for further investigation after ICH with age, deep location and hypertension used to diagnose “hypertensive ICH” and guide further testing[66]. Recent data clearly shows that the presence of cerebral SVD on an admission CT scan predicts a low yield of a macrovascular cause and can help guide clinicians as to the likely yield of IADSA[67] (see Figure 2). Several scores, including the recently validated DIAGRAM score[22], use simple clinical characteristics (age, location of ICH, signs of SVD) in addition to CT-angiography, aiming to predict the likelihood of macrovascular bleeding sources to guide further investigations. Additionally, several non-contrast CT markers[68] and the CT-angiography spot sign [69] have been proposed to identify patients at increased risk of hematoma

expansion (HE), but do not seem to sensitively identify the majority of patients at risk of HE; their value in clinical practice remains unproven

A comprehensive diagnostic work-up of ICH etiology is needed in ICH survivors to inform patients and relatives about the risk of recurrence as well as strategies for secondary prevention (i.e. possibly avoiding long-term anticoagulant medication in patients with severe CAA, and intensive blood pressure control in patients with deep perforator arteriopathy but also those with lobar ICH)[70]. MRI is superior in detecting markers of SVD[71] including white matter lesions, lacunes, perivascular spaces, cerebral microbleeds, cortical superficial siderosis and atrophy. A comprehensive work-up of ICH etiology should therefore include an MRI in the days/weeks following ICH onset including T2/FLAIR, DWI and SWI/T2* sequences. The underlying etiology has clear implications for the prognosis and future event rates after the acute ICH. A meta-analysis of 1306 patients with spontaneous ICH showed a higher recurrence rate for ICH in patients with CAA-related ICH compared to those with CAA-unrelated ICH (7.4% versus 1.1% per year)[72]. Additionally, multiple cerebral microbleeds (CMB) at baseline were associated with increased recurrence risk in both patients groups [72]. These are potentially helpful factors to predict prognosis as well as help management in specific patients, but further studies in larger populations worldwide are needed. The value of the newer Edinburgh criteria, summary SVD scores, and genetic factors for assessing prognosis (including recurrence rates and functional outcome) after ICH also require further investigation[27,73].

3. Acute treatment of ICH

The following treatment recommendations include information from the latest guidelines from the European Stroke Organization (ESO, 2014)[74] and the American Heart/Stroke Association (AHA/ASA, 2015)[75,76].

In general, patients with ICH should ideally be treated in a comprehensive hospital setting involving a multi-disciplinary team including neurology, neurosurgery, neuroradiology, intensive care, emergency medicine, and internal medicine (see Figure 3).

Key initial information to be obtained as soon as possible after admission to hospital (because they have immediate management implications) include the following:

1. Does the patient have elevated (>150mmHg) systolic blood pressure?
2. Is the patient taking anticoagulants?
3. Does the patient have intraventricular extension of the ICH with signs of hydrocephalus?
4. Is the patient at high risk for hematoma expansion (HE)?
5. Is there evidence of a macrovascular bleeding source (i.e. arteriovenous malformation, dural arteriovenous fistula, aneurysm, cerebral venous sinus thrombosis)?

These potentially treatable factors are all associated with early deterioration and poor functional outcome[77-81]. Up to 47% of patients deteriorate at some stage after the initial hemorrhage, but mostly within the first 24 hours; clinical deterioration itself is associated with poor functional outcome after ICH[79,81,82]. Many prognostic factors of poor outcome (such as age, volume and location of ICH) are non-modifiable[60,77,83] making it especially crucial to identify the modifiable factors listed above[84-87]. HE is a key potential treatment target and it is associated with several modifiable factors. Importantly, most HE occurs very early, suggesting that just as for ischemic stroke, “time is brain” for the treatment of ICH[80]. A recent individual-patient data meta-analysis shows that HE is significantly associated with time from onset of symptoms to baseline imaging, intracerebral hemorrhage volume on baseline imaging, antiplatelet and anticoagulation use[88]. It has previously also been associated with high blood pressure[89]. However, these factors are not the only predictors of HE, which can occur even in their absence.

3.1. Acute medical management

3.1.1. Stroke Unit care

A meta-analysis demonstrated that the decrease in death and dependency rate in patients with ICH admitted to a stroke unit is comparable to the effect in patients with ischemic stroke[90]. Thus, patients with ICH should be admitted to a stroke unit. Observational data suggest that treatment of patients with ICH in neurological intensive care units is also beneficial [91-93]. This positive effect of stroke units or

neurological intensive care units might be mainly due more frequent monitoring, early detection of complications and targeted treatments[94]. Thus, all ICH patients should be admitted as soon as possible to an acute or hyperacute stroke unit; those at high risk of neurological deterioration or requiring other body systems support should be transferred to a critical care setting, though evidence for which patients will benefit is lacking. Furthermore, early do-not resuscitate (DNR) orders (e.g. in the first 24 hours) should be avoided in the majority of ICH patients because they can lead to early palliation, precluding stroke unit admission and independently increasing mortality even after adjusting for clinical stroke severity[17].

3.1.2. Acute blood pressure lowering

Blood pressure is substantially raised compared to usual premorbid levels in patients in the days leading up to ICH[95], suggesting short term variability might be a key factor in ICH. Elevated systolic blood pressure at hospital admission is associated with HE, clinical deterioration, and mortality in patients with ICH[96-98]. Blood pressure management in ICH remains controversial with recent randomized controlled trials (RCT) reporting apparently conflicting results. The INTERACT 2 trial compared intensive treatment (defined as <140mmHg within 1 hour) with guideline-recommended treatment (target level of <180mmHg)[99]. The primary outcome in this study was death or disability (defined as a modified Rankin scale score [mRS] of 3-6) at 3 months. The primary analysis using a dichotomized statistical comparison showed a trend for a beneficial effect of the intensive treatment arm (odds ratio 0.87; 95% confidence interval [CI], 0.75 to 1.01; P = 0.06). Secondary analysis using ordinal shift analysis found a statistically significant reduction in the primary outcomes (odds ratio 0.87; 95% CI, 0.77 to 1.00; P = 0.04). The RCP guidelines (Edition 2016) recommend that patients with ICH who present within 6 hours of onset and a systolic blood pressure above 150mmHg should be treated urgently with a target blood pressure of 140mmHg or less at least 7 days. The ATACH-2 trial[100] compared intensive blood pressure lowering (target 110-139mmHg) with standard treatment (defined as 140-170mmHg) using intravenous nicardipine within 4.5 hours of onset. The primary outcome was death or disability (defined here as a mRS score of 4-6) at 3 months. The study was stopped prematurely after a pre-planned interim analysis showed no difference in death or disability rate in the intensive treatment

group (relative risk, 1.04; 95% confidence interval, 0.85 to 1.27). Furthermore, the risk of renal adverse events was significantly increased in the intensive treatment group compared to the standard treatment group (9% vs 4%, p=0.002).

There were differences between INTERACT-2 and ATACH-2 that might help explain the differences in results on ICH outcome. INTERACT-2 recruited nearly 2500 patients while ATACH-2 was stopped after 1000 patients. The choice of blood lowering treatment was left to the decision of the treating physician in INTERACT-2 while only intravenous nicardipine was allowed in ATACH-2. Most importantly, achieved blood pressure levels differed significantly: in INTERACT-2, after 1 hour, the mean systolic blood pressure level was 152mmHg in the intensive treatment group and 164mmHg in the standard treatment group, while in ATACH-2, the mean minimum systolic blood pressure during the first 2 hours was 129mmHg in the intensive treatment group and 141mmHg in the standard-treatment group. In other words, the standard treatment group in ATACH-2 had lower systolic blood pressure levels than the intensive treatment group in INTERACT-2. Two recent meta-analysis using aggregate data[101,102] combined the results of these (and other) trials, but these are of limited clinical relevance given the major differences between the INTERACT-2 and ATACH-2 trials. A subanalysis of ATACH-2 found that by lowering the blood pressure below 120-130mmHg the benefits of preventing haematoma expansion were offset by increased cardio-renal adverse events[103]. Large-scale individual patient data analyses of the INTERACT-2 and ATACH-2 trial data are awaited.

Although there has been concern that intensive blood pressure lowering might result in ischemic brain damage or other ischemic complications (i.e. acute coronary events), both INTERACT 2 and ATACH-2 reassuringly showed no evidence to support these concerns. On the other hand, data from observational studies found that about 25% of patients with ICH have acute ischemic lesions diagnosed using diffusion-weighted imaging (DWI) and this was associated with acute blood pressure lowering and in turn with poor outcome[104]. The prevalence, mechanisms and significance of DWI lesions in ICH remain controversial.

In summary, current evidence suggests that acute blood pressure lowering is safe, and reduction to below 140mHg according to the INTERACT-2 trial criteria has a modest beneficial effect on functional outcome. To avoid any deleterious effects, in our opinion it is reasonable in clinical practice to recommend an acute systolic blood pressure target of 130-140mmHg. Blood pressure fluctuations should be avoided and intravenous agents with short half life time are recommended.

3.1.3. Hemostatic agents (tranexamic acid and activated Factor VIIa)

Preventing HE using hemostatic agents in patients with ICH not associated with the use of anticoagulants (for this question please see the following chapter 3.1.4) has been a major treatment target and research topic in recent years[105]. Several trials evaluated the usefulness of activated Factor VIIa. They found that although it reduces HE, it is associated with an increased number of thromboembolic complications ultimately outbalancing the benefits[105]. Tranexamic acid (TXA) is an anti-fibrinolytic agent used to stop traumatic and post-partum bleeding complications. The recently published large international multi-center TICH-2 trial (Tranexamic acid for hyperacute primary IntraCerebral Hemorrhage), investigated whether intravenous TXA given within 8 hours of symptom onset reduces death and disability (using ordinal regression analysis of the mRS score). The trial did not show a significant difference of 3-month functional outcome between the TXA and placebo arm[106]. Interestingly – and in contrast to prior trials with activated Factor VIIa, - TXA was not associated with an increased risk of thromboembolic complications; the rate of serious adverse events was lower in patients receiving TXA than those receiving placebo. The trial showed a very modest reduction in HE and early death, but the clinical relevance of these findings remains uncertain given the lack of influence on functional outcome. TICH-2 had several limitations including a pragmatic, inclusive design which might have led to the inclusion of patients with large ICH in whom the reduction of HE might only have very limited effect on the overall (poor) prognosis. It remains plausible that TXA has a small treatment benefit requiring even larger trials; it is also possible that TXA might be usefully combined with other interventions including intensive blood pressure lowering (since subgroup analyses suggested those with lower BP at randomization might benefit most from TXA).

3.1.4. ICH associated with oral anticoagulants or antiplatelet agents

Antithrombotic therapy – i.e. anticoagulants (i.e. heparins, Vitamin K antagonists [VKA], direct oral anticoagulants [DOAC]) or antiplatelet agents (i.e. aspirin, clopidogrel) – are frequently used in elderly patients with vascular risk factors (i.e. atrial fibrillation, hypertension, diabetes mellitus) and a history of ischemic stroke or myocardial infarction. The overlap of risk factors for ischemic stroke and intracerebral hemorrhage and the resultant balance of ischemic and hemorrhagic risk is a central clinical dilemma in stroke medicine. Indeed, nearly 50% of patients with ICH are taking any antithrombotic medication[12]. Antiplatelet agents are independently associated with increased mortality[107] while oral anticoagulation is associated with an increased risk of HE and worse functional outcome[89,108]. Normalization of coagulation is a primary treatment goal in these patients.

The PATCH trial[109] investigated, whether in patients with antiplatelet-associated ICH, platelet transfusions, compared to standard treatment, reduces death and disability. Contrary to what was expected, the odds of death and dependence at 3 months was higher in the platelet transfusion group compared to the standard care group (adjusted common odds ratio 2.05, 95% CI 1.18–3.56; p=0.01). Therefore, platelet transfusion is not recommended in patients with antiplatelet-associated ICH. In patients with VKA-associated ICH, early and aggressive reversal of anticoagulation and blood pressure control was associated with improved outcomes in observational studies[110]. A small randomized controlled trial (INCH) showed that in patients with VKA-associated ICH, prothrombin complex concentrate (PCC) is superior to fresh frozen plasma (FFP) in normalizing the international normalized ratio (INR), and faster INR normalization seemed to be associated with smaller HE[111]; the optimal dosage of PCC for reversal is 25-50 U/kg IV[112].

In many healthcare systems, DOACs (apixaban, dabigatran, edoxaban and rivaroxaban) are now well established as first line treatments for patients with atrial fibrillation[113] and other settings (e.g. venous thromboembolism). Observational data reported conflicting results regarding outcome of DOAC-associated ICH compared to VKA-associated ICH with some studies finding only little difference[114] whilst others reported better outcomes and less HE in patients on DOAC[115,116]. However, a recent

pooled analysis found that despite the lack of specific reversal agents, DOAC-associated ICH was not worse (and might be better) than VKA-associated ICH [116]. Recent data suggest that treatment with coagulation factors (PCC) might not prevent HE in patients with DOAC-associated ICH[117]. Idarucizumab is an antibody fragment developed to reverse the anticoagulant effect of the DOAC dabigatran. The REVERSE-AD study[118,119], a single arm open label study in patients taking dabigatran with major bleeding or in need for urgent surgery, found that the measurable effect of dabigatran in the blood (i.e. measured with a drug-specific assay) can be totally reversed within minutes after administration of idarucizumab. The rate of thromboembolic complications at 90 days was about 7% and the mortality was about 18%.

Andexanet alfa is a recombinant modified human factor Xa decoy protein that was designed to reverse the effect of factor Xa inhibitors (i.e. the DOACs apixaban, edoxaban and rivaroxaban). The ANNEXA-4 study[120], which had a comparable design to REVERSE-AD, was a single arm open label study in patients taking apixaban or rivaroxaban with major bleeding. They found that the anticoagulant effect was rapidly reversed after administration of andexanet alfa. However, a concern was that thromboembolic complications occurred in 18% of the patients; 15% of the patients died within 3 months [112].

Both specific reversal agents – idarucizumab and andexanet alfa – showed favorable pharmacological results. Unfortunately, due to the design of the studies (single arm, open label), no firm conclusion about the clinical effect of these drugs in acute ICH can yet be made. Due to lack of clinical equipoise, it is unlikely that a randomized trial using these agents will be conducted. In addition, there might be economic challenges with both treatments: a single dose is estimated to cost around $3000 for idarucizumab and $30’000 to $60000 for andexanet alfa[121-123].

There is currently one ongoing RCT, investigating whether TXA in addition to standard care (which may include the use of idaricuzumab or andexanet alfa if deemed appropriate) is effective in preventing HE in patients with DOAC-ICH (TICH-NOAC, ClinicalTrials.gov Identifier: NCT02866838). Results are expected in 2020.

To summarize, for antiplatelet-associated ICH, antiplatelet transfusion is not recommended. By contrast, fast reversal of the anticoagulant effect in anticoagulant-associated ICH is mandatory. While for VKA-associated ICH PCC treatment seems to be superior to FFP, data for the treatment of DOAC-associated ICH are scarce; although the use of PCC seems reasonable, no firm evidence-based recommendations can currently be made. Specific reversal agents are promising but there is currently no data available regarding clinical efficacy to prevent hematoma expansion or improve outcome in DOAC-associated ICH. However, as they are available and preliminary data suggest a reasonable safety profile, they should be considered for treatment of DOAC-associated ICH. Further studies are warranted to definitively determine whether they are definitely safe and clinically effective.

3.2. Surgical Management

3.2.1. Supratentorial versus cerebellar hemorrhage

Supratentorial intracerebral hemorrhage is generally managed conservatively because the indications for, and clinical benefit of surgical evacuation remain controversial. Given the overall poor outcome in patients with ICH considered for surgery, the prognosis and goals of care should always be discussed with patients, caregivers and family members. The standard in surgical intervention remains open craniotomy[75]. The largest RCT to date, the STICH I trial, including 1033 patients with a supratentorial ICH, was aimed to compare early surgical treatment to the best available treatment[124]. It did not demonstrate a difference of 6-month favorable functional outcome or mortality in the surgical group compared to the medical group (26% versus 24%, $p = 0.41$). Surgical management was chosen by the treating neurosurgeon; however, in 77% a craniotomy was performed. The sub-group analysis of superficial lobar ICH demonstrated an 8% absolute increase in favorable functional outcome comparing the interventional and medical group ($p = 0.02$)[124]. The following STICH II trial conducted by the same group was designed to evaluate the potential positive subgroup findings of the STICH I trial[125]: STICH II recruited 601 patients with superficial lobar ICH, volumes of 10-100ml, location <1cm of the surface of the brain and no IVH. 307 patients were assigned to the early surgery arm and 294 to the initial conservative arm. Somewhat disappointingly, functional outcome was not significantly different

between the surgical (hematoma evacuation within 12 hours of randomization) and conservative arm, although a trend of decreased 6-month mortality in the surgical arm in patients with a GCS >8 existed[125]. A further meta-analysis, including STICH II, which demonstrated a beneficial influence of early surgery. However, heterogeneity between the 15 included trials was significant (p=0.0002)[125].

In recent years, the potential role of minimally-invasive evacuation of ICH has been investigated. Trials evaluating the role of minimally-invasive surgery include the MISTIE trials[126-128]. Other groups have made an effort to improve techniques for the minimally-invasive endoscopic approach, such as the SCUBA technique [129]. The phase-II "minimally invasive surgery plus alteplase in intracerebral haemorrhage evacuation" (MISTIE II) trial investigated safety of minimal-invasive treatment via imaging-guided catheter evacuation of ICH with additional application of the thrombolytic substance alteplase compared to standard medical therapy. [130,131].. From the same group, the results of a large randomized phase 3 clinical trial (MISTIE III,) have recently been published[128]. There was no statistically significant difference between both treatment groups in good functional outcome (measured by an mRS of 0-3) after 365 days [128]. The exploratory secondary results suggest that hematoma volume reduction to 15 mL or less in the intervention group was associated with better functional outcome in patients who were stabilized. There is currently no evidence for this approach to be used routinely. .

Observational studies[132,133] suggested reasonable safety and potential clinical benefit of hemicraniectomyfor space-occupying ICH. The aim is not to remove the hemorrhage but to give the brain more space, decreasing pressure by decreasing mass effect, thereby hopefully preventing secondary injuries and improving functional outcome. The ongoing "Decompressive Hemicraniectomy in Intracerebral Hemorrhage" (SWITCH) trial (NCT02258919) compares decompressive craniectomy and best medical management with best medical management alone in ICH located in the basal ganglia or thalamus. The primary outcome of this study is functional outcome with secondary outcome being mortality, dependency and quality of life. Results are expected in the next years. The decision whether to operate or not and if to operate how, therefore remains controversial and decisions are still taken on

an individual basis. Results from future trials on minimal invasive (endoscopic) surgery like from the SWITCH trial could significantly alter guidelines and recommendations on how to treat supratentorial ICH.

The approach to infratentorial ICH seems more straightforward. Intracerebellar hemorrhage constitute about 10% of spontaneous ICH[134]. Due to the confined space in the posterior cranial fossa relatively small mass lesions can have life-threating complications due to brainstem compression, hydrocephalus and consequently early neurological deficits, including lower cranial nerve palsies, impaired consciousnesses level, coma, including respiratory failure, and death[135]. They are a neurosurgical emergency and the threshold for evacuation is low. Patients with a cerebellar ICH of >3 cm and patients with a smaller cerebellar ICH but resulting hydrocephalus or brain stem compression should be treated surgically, namely posterior decompressive evacuation and or ventricular catheter placement[136,137]. Ideally patients should be operated while they still have a relatively good neurological state[138,139]. However, current management is based mainly on retrospective studies and results are controversial. Although some studies show an improvement in morbidity and mortality in patients who underwent evacuation for cerebellar ICH[140], others confirm surgical treatment as life-saving but with an increased tracheostomy rate and poor functional outcome[141,142]. A prospective randomized controlled trial seems unlikely due to lack of clinical equipoise.

3.2.2. Timing of surgery

The optimal timing of surgery for ICH is uncertain and practice is wide-ranging [124,143,144]. A previous individual patient-data meta-analysis reported an improved outcome when surgery was performed within 8 hours, with another study indicating very early surgery within 4 hours from onset not being beneficial and even harmful[145,146]. However, evacuation might be considered as a life-saving measurement in deteriorating patients independently of the timing. Thus, although routine surgical evacuation of ICH is not recommended, when indicated, early surgery might have a specific role [147].

3.2.3. Coexisting intraventricular hemorrhage

Intraventricular hemorrhage is an independent predictor of poor functional outcome after ICH and occurs in 45% of patients with ICH; it potentially leads to hydrocephalus, which decreases the likelihood of favorable functional outcome even further[148,149]. When IVH is complicated by hydrocephalus patients may profit from the insertion of an extraventricular drain (EVD) as reduced mortality has been reported[150,151]. Previous studies have investigated the influence of fibrinolytic agent application on functional outcome and mortality in patients requiring EVD. EVD insertion seems to increase clearance rate of the intraventricular blood as well as to decrease mortality improve functional outcome[152-154]. A recent randomized, double-blinded, placebo-controlled trial, the CLEAR III trial, however, investigated the influence of alteplase application in patients with routinely placed EVD's[126]. They reported a reduction in mortality in patients undergoing alteplase irrigation, however functional outcome was not improved; the rate of severe disability in survivors was actually very high[126]. Despite this disappointing result, not all possible aspects have been investigated. A quicker and more complete removal of the clot, enhanced by an exact, potentially imaging-guided EVD placement still holds promise and will hopefully be the target of future trials. Evidence exists that serial neuroimaging as well as frequent neurological examination help in determining patients that were initially considered to not need surgical intervention (EVD insertion or craniotomy)[155]. Nevertheless, we have to bear in mind that an EVD is an invasive procedure with potential complications. The role of fibrinolytic agents on functional outcome in patients with EVD after ICH remains unclear[147].

3.2.4. Intracranial pressure monitoring

Intracerebral hemorrhage can lead to increased intracranial pressure (ICP). Which patients require ICP monitoring as well as treatment remains unclear as no RCT or other evidence-based guidelines exist[147].

3.3. Secondary prevention of ICH and management of antithrombotics

3.3.1 Antithrombotics: oral anticoagulants and antiplatelets

Patients with ICH are at risk not only of recurrent ICH but are also at similar risk of ischemic stroke and other vaso-occlusive events[1]. Atrial fibrillation (AF) is found in about 20% of ICH survivors and

causes a particular treatment dilemma as oral anticoagulation reduces ischemic stroke risk in AF by about 70%[113] but is likely to increase the risk of recurrent ICH. Recent observational studies suggest that restarting anticoagulation might have net clinical benefit in ICH survivors with AF: some suggest little difference in the risk of recurrent ICH between patients with ICH and atrial fibrillation who were restarted on anticoagulation and those who were not[156,157], but with a significantly reduced risk of ischemic stroke when OAC was restarted. These studies were based on observational data and are likely to be affected by selection bias and unmeasured confounders. The effect on the risk of ischemic stroke or intracerebral hemorrhage might differ by ICH location (deep vs. lobar) and acute (CAA vs non), though some observational data suggest that restarting OAC might have a favorable outcome regardless of ICH location[156].

Several RCTs investigating the use of antiplatelets or oral anticoagulants (COCROACH collaboration: RESTART [ISRCTN71907627], RESTART-FR [NCT02966119], STATICH, APACHE-AF [NCT02565693], NASPAF-ICH [NCT02998905], SoSTART [NCT03153150], A3-ICH and ASPIRE; a further European collaborative trial (PRESTIGE-AF) has also been commenced. Although at this moment no clear recommendation can be made, these trials will hopefully provide valuable insights into whether, and when, antiplatelets or anticoagulants in patients after ICH and a clear indication for anticoagulant or antiplatelet treatment should be used. Enrolment of suitable patients in these trials is recommended whenever possible. However, in patients with ICH and atrial fibrillation judged at extremely high risk of recurrent ICH on long term oral anticoagulation (e.g. those with severe CAA), closure of the left atrium appendage is a potential alternative[158] that avoids the need for long term OAC. In patients with mechanical heart valve, observational data suggest that restarting 2 weeks after ICH is reasonably safe, while in patients judged at high risk of thromboembolic events, re-starting as early as 7 days after ICH could be considered[159].

3.3.2. Statin therapy

The “Stroke Prevention by Aggressive Reduction in Cholesterol Levels” (SPARCL) trial initially raised concern that statins might increase the risk for future ICH among patients with previous ischemic stroke or ICH [160]. While some studies also suggested an increased recurrent ICH risk in ICH survivors using

statins [160-163], others suggest that statins used acutely are associated with improved mortality and functional outcome [164,165]. A recent meta-analysis of statin use in stroke survivors found no evidence that statin use in ICH survivors increases future ICH; there was a small increased risk of ICH after ischemic stroke; however, the strongest finding was that in all stroke survivors (ischemic stroke or ICH) there was a substantial and significant improvements in mortality and functional outcomes among statin users[166]. The role of statin therapy in ICH survivors remains controversial, but in our opinion, there is currently no strong evidence to withhold statins in survivors of ICH. Randomized trials are needed to address this important clinical question.

3.3.3 Long term blood pressure lowering therapy

Evidence from trials investigating blood pressure lowering in patients with ischemic stroke found that elevated blood pressure is associated with increased risk of ICH[167]. The SPS3 trial in patients with small subcortical strokes attributed to cerebral small vessel occlusion showed that more intensive blood pressure control significantly reduces the risk of ICH by nearly 70%[168]. In a sub-analysis of PROGRESS (including patients with ischemic stroke and ICH), the lowest achieved blood pressure levels were associated with the lowest risk of ICH[169,170]. The benefit of blood pressure lowering was substantial, including in patients with probable CAA, though the number of participants with ICH was small[171].Observational data also suggest that lower blood pressure is associated with a lower risk of recurrence, for both lobar and deep ICH[170]. Based on these data, current guidelines recommend a treatment target of 130/80 mmHg after ICH. However, no randomized controlled trial has yet specifically investigated the effect of long-term intensive blood pressure control for secondary prevention after ICH. There are currently ongoing randomized trials investigating triple antihypertensive therapy (TRIDENT: NCT02699645) and telemetry-guided intensive treatment (PROHIBIT-ICH; https://www.ndcn.ox.ac.uk/research/prohibit-ich) specifically in ICH survivors. These should help define the target and optimal strategy for long term BP control after ICH.

3.3.4 Experimental treatments and neuroprotection

Secondary neuronal injury in ICH is mediated through different mechanisms[172] including the toxic effects of iron (from lysed blood) and inflammation. Beyond the aforementioned treatment strategies,

translational research has focused on strategies for neuroprotection in ICH. So far, no promising candidate target has been tested in a large phase 3 trial. However, several potentially promising targets have been tested in phase-II trials with mixed results:

Iron from hemolysed blood is implicated in secondary injury after intracerebral hemorrhage. A recently published phase 2 placebo-controlled, double-blinded trial (the i-DEF trial) investigated safety of the intravenous iron chelator deferoxamine mesylate in ICH patients and its potential influence on good functional outcome (measured by an mRS of 0-2)[173]. Although the application is safe, it did not show an influence on good functional outcome when compared to placebo (saline infusion) and therefore a phase 3 trial, is not recommended [173].

Recent research elucidated the role of neuroinflammation and the immune system in ICH [174] and its role in formation of perihematomal edema and secondary brain damage. Different immunomodulatory strategies are being explored. A phase-II randomized controlled trial found fingolimod, a sphingosine 1-phosphate receptor modulator approved for multiple sclerosis, to be safe, reduce perihematomal edema, attenuated neurologic deficits, and promote recovery[175].

Interleukin-1 (IL-1) is a pro-inflammatory cytokine which could be a target for neuroprotection by reducing neuronal injury[176,177]. Interleukin-1 Receptor antagonist (IL-1Ra) has been demonstrated to be neuroprotective in ischemic stroke models and to reduce peripheral inflammation in patients suffering from aneurysmal subarachnoid haemorrhage[177]. The SCIL-STROKE (subcutaneous interleukin-1 receptor antagonist in ischemic stroke) is a recent phase 2 RCT on IL-1Ra investigating its effect in ischemic stroke[178]. IL-1Ra was not associated with favourable outcome despite it reducing plasma inflammatory markers. However, inflammation may not necessarily be a negative phenomenon in acute ICH[179] and there is interesting data on stroke-induced immunodepression and secondary complications after ICH[180]. The soon to be starting BLOC-ICH trial (NCT03737344) is a randomized, double-blinded, placebo-controlled Phase II clinical trial investigating the effect of an IL-1Ra on inflammation and brain swelling in ICH patients. This trial will help to assess and understand the role of inflammation in ICH specifically and evaluate it as a potential target. First results are awaited for 2020.. Another example is Haptoglobin (Hp). Hp, an acute-phase protein, is involved in the Hemoglobin-Haptoglobin-CD163 scavenging process: it binds free hemoglobin (Hb) and consequently

inhibits the breakdown of Hb into heme and iron, thus potentially preventing its toxic and inflammatory effects[181-184]. Hp might be associated with functional outcome after ICH through modulation of inflammation and therefore be a drug target in the near future. A full discussion of other neuroprotective approaches is beyond the scope of this review.

Another important perspective for future trials includes imaging-based selection of candidates for acute treatment strategies to prevent haematoma expansion, for example using the spot-sign and/or recently described non-contrast CT signs[69,185].

4. Conclusions

When a patient arrives at the hospital, emergency brain imaging to diagnose ICH and detect intraventricular extension with hydrocephalus or macrovascular bleeding sources is important for timely intervention. Just as for ischemic stroke, in acute ICH “time is brain” and prompt treatment to target hematoma expansion and other acute modifiable factors (e.g. perihematomal edema, inflammation) seems most likely to improve survival and outcome. All treatable factors (i.e. elevated blood pressure, anticoagulation reversal) should be addressed immediately and simultaneously.

However, many management aspects remain unclear, such as indications for surgery. Several fundamental questions regarding secondary prevention require further evidence, including the restarting of antithrombotic drugs, blood pressure control and statin use. There is a need for better phenotyping of ICH according to the underlying arteriopathy; such understanding should help with not only acute treatment targets but also rational primary and secondary prevention strategies.

5. Expert commentary

In recent years, significant advances have been made in the causes, diagnosis, classification, pathophysiological understanding, treatment and prevention of ICH. MRI is increasingly used to visualize markers to diagnose of the underlying arteriopathy (CAA or deep perforator arteriopathy). In the absence of MRI, CT and the APOE genotype may help to diagnose CAA in acute patients with

severe ICH. Acute blood pressure lowering is safe and very likely beneficial, but some controversy remains about the exact target level and size of treatment effect. Earlier treatment combined with other therapeutic approaches (e.g. hemostatic, Hb scavenging/chelation, or anti-inflammatory treatments) could be even more effective. In ICH associated with oral anticoagulants rapid reversal (with coagulation factors (PCC) or specific agents) is essential, though randomized controlled trials of specific NOAC reversal agents are lacking. Tranexamic acid is safe and reduces hematoma expansion but does not improve functional outcome at 3 months so cannot be recommended as routine therapy for ICH. It remains to be shown whether TXA in combination with other interventions (e.g. acute BP lowering, surgery) might show a benefit, or whether there is a small but worthwhile treatment effect of TXA alone. Platelet transfusion is not recommended in patients with antiplatelet-associated ICH as it has been shown to increase the odds of death and dependence at 3 months[109]. Only a minority of patients with supratentorial ICH require surgery; although patients with a superficial sICH or patients with a GCS of 9-12 may benefit, but the timing remains unclear.

However, the clinical outcome from ICH remains poor and many challenges remain. Better understanding of disease pathways from genetic studies, improved prognostic tools, combined acute interventions (including medical therapies targeting hematoma expansion, inflammation, edema, minimal-invasive surgery, and hemicraniectomy where indicated) and prevention trials should further improve clinical outcomes and prevention of this devastating disease.

6. Five-year review

- Acute brain imaging will be augmented by deep learning algorithms to identify the causal arteriopathy, risk for hematoma expansion, and prognosis [186].
- As for ischemic stroke, time is brain in acute ICH treatment; increasingly rapid treatment pathways will be established in clinical practice and trials.
- New therapeutic strategies targeting perihaematomal edema, inflammation, neuroprotection, hemoglobin toxicity and scavenging should become useful adjuncts to therapies targeting

hematoma expansion; a combined approach including established therapies (BP lowering, OAC reversal) and these new modifiable factors is most likely to be beneficial.

- Minimally invasive surgery (with new devices and protocols) is likely to play an increasingly important role to improve survival and functional outcome.
- Decompressive hemicraniectomy might be a helpful treatment for space-occupying ICH with raised intracranial pressure
- A key remaining issue is outcome prediction as currently available scoring systems (i.e. ICH-score[187]) have limited performance, and have not been evaluated for longer-term outcome; detailed capture and analysis of multimodal high-dimensional brain imaging, clinical and genetic data will allow more accurate assessment of prognosis for future vascular events and functional outcome, leading to tailored secondary prevention.
- Currently, several RCT investigate, if, how and when oral anticoagulants or antiplatelet agents should be used after ICH. Tailored risk assessment and therapy will become routine.
- Long-term intensive BP lowering will be offered, using home telemetry and wearable devices or, where such technology is not readily available, a combined antihypertensive "polypill" approach.
- Improved understanding of causal mechanisms will allow true disease-modification of SVD progression in addition to treating known risk factors such as hypertension.
- Primary prevention of ICH will be improved, for example by improved population blood pressure control and personalized use of antithrombotics guided by better biomarkers of intracranial bleeding risk[188].

Funding

This paper was not funded.

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FIGURE LEGEND

Figure 1. A) Modified Boston criteria, B) CT Edinburgh criteria

Figure 2. Pathway to decide on intra-arterial digital subtraction angiography to further investigate ICH cause

Figure 3. ICH care pathway