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THE HAEMATOMA EXPANSION PARADOXES

A study of haematoma expansion in

acute primary intracerebral haemorrhage

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INDEX

ABSTRACT

Introduction: intracerebral haemorrhage (ICH) accounts for approximately 10-15% of all new strokes that occur each year, but results in disproportionately high morbidity and mortality. Outcome has not improved significantly in recent decades due to the lack of clear beneficial medical or surgical therapies. One of the four factors thought to be responsible for the praecox clinical and radiological deterioration of ICH patients is haematoma expansion (HE). Aims of our study were to analyze the haematoma expansion phenomenon, any risk factors and its influence on outcome, and to evaluate ICH patient characteristics, investigating elements that could contribute to determining ICH outcome. **Methods**: we conducted an observational longitudinal study on retrospectively collected data on 206 consecutive patients with primary or anticoagulant-associated ICH admitted to the Stroke Units of the Neurology Units of Treviso Hospital and St. Anthony's Hospital of Padova, from January 2011 to December 2015. Patients with a secondary cause of ICH were excluded. We recorded baseline history, radiological, laboratory and clinical admission data, and follow-up information. **Results**: our ICH population was characterized by elderly Caucasian patients with a slight prevalence of males, small haematoma volumes and mild-moderate clinical severity. While male patients seemed to have a higher incidence of ICH, at a younger age, with a different vascular risk-factor profile and a higher risk of haematoma expansion, outcome was not poorer than in female patients. Of our population, 28.6% presented significant HE and the risk factors for HE proved to be male sex and higher NIHSS score. At follow up, mortality was 24.7% at three months and 28.4% at one year; based on the mRS, the average patient was dependent at three months. At follow up, there was a slightly higher percentage of ICH relapses than of ischemic strokes. Age, haemorrhage characteristics, as baseline volume and ventricular invasion, haematoma expansion and clinical severity are the strongest predictors of outcome. **Conclusions and Discussion**: the analysis has confirmed the complexity of the haematoma expansion phenomenon, which still remains partially unknown. Our findings have yielded several paradoxes and we wonder

whether haematoma expansion can be truly considered a prognostic factor or represents one step in the natural history of every ICH. Considering the natural history of ICH patients, none of the identified prognostic factors is modifiable at the time of medical evaluation. ICH pathology and the haematoma expansion phenomenon are still not sufficiently understood and more studies are warranted to positively influence the prognosis of these patients.

1. INTRODUCTION AND REVIEW OF THE LITERATURE

PRIMARY INTRACEREBRAL HAEMORRHAGE

1.1 Epidemiology:

First described by Morgagni in 1761, primary intracerebral haemorrhage (ICH) accounts for approximately 10-15% of all the new strokes that occur every year[21], with an annual incidence of 24.6 per 100.000[137]. Incidence is substantially variable across countries and ethnicities: African Americans, Chinese, Japanese and Koreans (who have a high frequency of hypertension) have higher frequencies of ICH1[39], the incidence rates in low and middle-income countries are higher than in high-income countries (ICH accounts for 10% of stroke in high-income countries and 20% in low-income countries)[40], and have not decreased over recent years[1]. Moreover, incidence increases with age and several studies have shown sex differences in incidence and pathophysiology in primary ICH[1,50,66,149], with a higher male incidence; European studies have not confirmed sex differences in overall ICH incidence with two exceptions: a male predisposition in Greece and Norway[50,120,156]. There is also conflicting evidence about the influence of sex on outcome after spontaneous intracerebral haemorrhage[34,66]. The case fatality rate of ICH is approximately 40% at 1 month (but varies substantially among countries), with half of the deaths occurring within the first two day post ictus, and 54% at 1 year, with only 12% to 39% of patients achieving long-term functional independence[1,16,41]. Although researchers' attention has been drawn by the high rates of morbidity and mortality of ICH, no significant improvements have been made to outcomes and prognosis in the last few decades and no medical or surgical therapy has yet proven to benefit clinical outcomes (mortality following ICH does not in fact differ significantly between different study cohorts examined more than a decade apart This reflects the lack of proven effective treatments for this condition)[41].

1.2 Causes and Pathogenesis[21]:

The most common cause of ICH is hypertension, and the relationship between hypertension and ICH is biphasic. ICH can present both at the onset of hypertension or in case of sudden blood pression elevation, and later, after the development of degenerative changes in vessel walls in the form of lipohyalinosis, fibrinoid degeneration and miliary (Charcot-Bouchard) aneurysms. When hypertension first develops, the small arteries and capillaries are exposed to a high head of pressure and can leak; on the other hand, ICH can develop in situations in which blood pressure increases abruptly (acute hypertension-related ICH), as during strong stimulus of the sympathetic system (dental procedures, use of illicit drugs with sympatheticomimetic effects, exposure to severe cold weather) or after sudden increase of cerebral blood flow (after carotid endoarterectomy or heart surgery). Later in the course of hypertension, haemorrhage into the brain parenchyma is often preceded by hypertensive damage to small cerebral penetrating arteries and arterioles: subintimal foam cells sometimes obliterate the lumens and pink-staining fibrinoid material lies within vessel walls. The arteries in spots are often replaced by whorls, tangles, and wisps of connective tissue which often obliterate the usual vascular layers. Fisher called these processes segmental arterial disorganization, fibrinoid degeneration and lipohyalinosis. Lipohyalinotic arteries could occlude, leading to lacunar infarct, or rupture, causing intracerebral haemorrhage. Small aneurysmal dilatations, first hypothesized by Charcot and Bouchard in the 1870s, represent weak points that break under increased arterial tension but, in many patients, abrupt elevation in blood pressure causes the rupture of small penetrating arteries that had no prior vascular damage. Leakage from these small vessels produces a sudden but local pressure effect on surrounding capillaries and arterioles, causing them in turn to break. In contrast with subarachnoid haemorrhage, ICH develops gradually with signs/symptoms that develop in the course of minutes/hours/days, with a potential window of intervention. Bleeding from small deep penetrating vessels is usually under arteriolar or capillary pressure (in contrast with SAH, in which arteries of the brain surface leak blood under systemic pressure). At the centre of the lesion there is a large mass of blood; as ICH develops,

pressure within the central core increases and compresses small vessels at the periphery of the haematoma. These capillaries and arterioles in turn break and blood escapes, enlarging the lesion (avalanche-type effect). The haematoma grows until equilibrium is reached between the pressure within the haematoma and surrounding pressure. The gradual increase in the size of the haematoma translates clinically into a gradual worsening of symptoms and signs. A large haemorrhage increases intracranial volume and pressure: when intracranial pressure increases, the venous pressure in the draining dural sinuses increases, and to perfuse the brain the arterial pressure must rise to produce an effective arteriovenous difference. Thus, patients with intracerebral haemorrhage may have markedly elevated blood pressure merely because of the haemorrhage which does not necessarily reflect the premorbid blood pressure (see below). Lowering the pressure helps to stop the bleeding but caution must be taken because the elevated pressure also serves to perfuse areas of the brain not damaged by the haemorrhage. In the very acute phase, as the blood collections are still discontinuous, blood dissects through otherwise normal brain tissue, presumably along a pressure gradient following the path of least resistance along blood vessels or along axons. In a second phase, the haematoma takes on an ovoid and then spherical shape[29]. Trauma, bleeding disorders and degenerative changes in congenitally abnormal blood vessels within vascular malformations may also initiate intracerebral bleeding, which then progresses in a manner similar to hypertensive intracerebral haemorrhage.

1.3 Evolution and outcome:

Multiple predictors of outcome and mortality after ICH have been identified, including patient age and Glasgow Coma Scale at presentation[56,116]. The most relevant aspect of ICH evolution is that clinical signs and symptoms often deteriorate within 24-72 hours of onset, and this deterioration is associated with haematoma expansion (accounting for the majority of acute progressing strokes), with the development of perihaematomal oedema, with the extension of ICH to the ventricular system, and with inflammation. Haematoma expansion could be a potentially modifiable factor that

correlates with poor functional outcome and death: it occurs in up to 40% of ICH and is caused by continued bleeding from the original source and injured surrounding blood vessels[17,25,47]. This percentage might suggest that not all patients have the same risk of haematoma expansion: identifying patients at greatest risk of expansion could provide opportunities to identify patients who may benefit from therapeutic intervention.

1.4 Haematoma expansion:

There is no universal consensus as to the definition of haematoma expansion and the most commonly used definitions are an increase in the volume of intraparenchymal haemorrhage of >33% between the baseline and the repeated CT scan, an increase of volume by ≥ 12.5 cm3 or by ≥ 1.4 times[36].

Table 2 Sensitivity and specificity of various cutoffs for prediction of poor outcome (mRS 4–6)[a]

Cutoff	Frequency, n (%)	Sensitivity, %	Specificity, %	PPV, %	NPV, %
≥3 mL	172 (32)	46	81	70	60
≥6 mL	125 (24)	35	88	74	58
≥12.5 mL	70 (13)	22	95	81	55
≥26%	159 (30)	40	79	65	57
≥33%	142 (27)	37	83	68	57

Abbreviations: mRS = modified Rankin Scale; NPV = negative predictive value; PPV = positive predictive value.
[a] n = 531.

Fig 1: from Dowlatshahi D et al. Defining haematoma expansion in intracerebral hemorrhage. Neurology 2011; 76: 1238-1244, Different HE definitions and their sensitivity/specificity in predicting a bad outcome.

All definitions of significant HE have much lower sensitivity than specificity for predicting poor outcome (<50%). Accordingly, the positive predictive values (the probability that a patient with HE will have a poor outcome) ranged from 66% to 78%. A clinically relevant definition of HE suitable for use as a surrogate marker in haemostatic therapy trials should have a high positive predictive value, meaning that there is a high likelihood that a patient meeting the definition for HE will have a poor outcome. In this context, the commonly used ≥ 12.5 mL cutpoint has the highest adjusted

odds ratio for predicting all poor outcome definitions and is above the minimal detectable difference (MDD) of quantitative volumetric ICH measurement[36].

1.4.1 Non radiological predictors of haematoma expansion:

The following non-radiological predictors of haematoma expansion have been proposed for investigation:

- **bleeding diathesis due to coagulopathies**[21], **liver disease**[68] **and alcohol consumption**[47]. Alcohol consumption has been proposed to contribute to haematoma expansion, partly through an effect on the lipid profile. A study by Pletsch et al evaluated the relationship between daily alcohol use, LDL and haematoma expansion: this study suggests that neither chronic daily alcohol use nor a low LDL level in combination with daily alcohol use can be used to predict ICH growth. A low LDL level in combination with daily alcohol use may be linked to larger, more severe ICH but the study could not demonstrate a relationship with haematoma expansion or poor clinical outcome[107].

- **Bleeding diathesis due to medical therapy**.

a) **antiplatelet therapy**: platelets have a central role in the haemostatic system: they adhere to the site of injury, aggregate and provide a procoagulant surface for rapid formation of a haemostatic plug. A relationship between prior antiplatelet agent use and increased risk of ICH and haemorrhage growth is thus biologically plausible. Several observational studies have shown a relationship between prior antiplatelet use and increased haematoma growth, worse outcome and mortality[16,101,121,136,151]. By contrast, other investigators could not demonstrate such a correlation, particularly after adjustment for confounding factors[44,93,122] and reported limited data on antiplatelet therapy type and combination therapy. Moreover, small studies of platelet infusion after intracerebral hemorrhage onset in patients with a history of antiplatelet use did not show a statistically significant benefit[28,39,97]. Experimental models in animals support this latter hypothesis and have failed to show a substantial effect of antiplatelet pretreatment on intracerebral haemorrhage volume[74], probably due to a tissue-specific role for platelets after vascular injury. In

particular, the brain pericytes lining blood vessels could also provide the procoagulant surface for interaction with coagulation cascade and, in ICH, these mechanisms could help compensate for impaired platelet function caused by prior use of antiplatelet agents use. A recent study by Khan NI and colleagues[69] suggested an association between previous use of dual antiplatelet therapy and in-hospital mortality for ICH patients when compared with no therapy, but did not show a correlation between single antiplatelet therapy and morbidity or mortality. This suggests that excess mortality risk associated with antiplatelet therapy is confined to those patients receiving dual therapy before ICH.

b) **warfarin use**: intracerebral haemorrhage is the most devastating complication of oral anticoagulation. The reported incidence of ICH in patients receiving anticoagulant therapy with warfarin is 7- to 10-fold higher than in patients not receiving warfarin therapy[45,158] and anticoagulant-associated haemorrhage currently accounts for nearly 20% of all intracranial haemorrhages[42]. Moreover, warfarin-correlated intracerebral haemorrhage has been associated with a poorer prognosis as compared to spontaneous haemorrhage[41]. Although warfarin-associated haemorrhages are usually classified as a secondary form of intracerebral haemorrhage, it is likely that the relationship between warfarin and ICH is not strictly causative: warfarin use is considered to increase a haemorrhage that would have developed in any case for different reasons (in amyloid or hypertensive angiopathy, due to trauma or vascular malformation) and represents a risk factor for increased volume and poor outcome. Supporting this hypothesis, older age and the presence of microangiopathy in warfarin-anticoagulated patients increase the risk of haemorrhage, suggesting that both spontaneous haemorrhages and warfarin-associated hemorrhages share the same etiopathogenetic substrate. MRI studies with GE sequences demonstrated the presence of asymptomatic microbleeds in older patients affected by hypertension. This finding corroborates the hypothesis that anticoagulation represent an aggravating factor in the development of ICH in an at-risk population. Considering that haematoma expansion is one of the determinants of outcome in ICH patients and considering that warfarin use has been demonstrated to worsen the outcome of

ICH patients, it has been speculated that anticoagulant therapy could facilitate haematoma expansion and thus influence the prognosis of these patients. Several studies have suggested this association[18,43,146], but they have some limitations (as considering the use of warfarin and not INR values in the acute phase). Studies and trials conducted on warfarin-associated intracerebral haemorrhage as a whole have failed to reach definitive conclusions on defining in particular whether haematoma size is larger in oral anticoagulant (OAC)-associated than in spontaneous ICH, and whether OAC-ICH patients have a higher percentage of haematoma expansion and a poorer prognosis than non-anticoagulated patients. Moreover, the effect of anticoagulant therapy is now difficult to evaluate because of strict recommendations from international guidelines to reverse warfarin and restore normal coagulation parameters using prothrombin complex concentrate or fresh frozen plasma in combination with vitamin K in the acute phase In particular, Flibotte JJ et al[43] investigated whether the reported increased mortality in OAC-ICH reflected increased baseline ICH volume or increased ICH expansion. They concluded that warfarin did not increase ICH volume at presentation but increased the risk of haematoma expansion, and that the raised mortality in OAC-ICH patients appeared to be mediated by haematoma expansion. In their observational prospective study, Horstmann et al[59] consecutively enrolled patients with supra- and infratentorial ICH and compared spontaneous ICH to OAC-ICH (defined as an ICH occurring in a patient treated with OAC at the time of ICH and with an INR $\geq$ 1.4). Of all ICH, 25% were related to OAC and the authors reported that, compared to patients with spontaneous ICH, OAC-ICH patients were older, more frequently had initial extension of ICH into the ventricles or isolated primary intraventricular haemorrhage. After correction for age, there was a trend towards a poorer outcome in OAC-ICH. In contrast, initial ICH volume and haematoma expansion did not differ between the two groups. Dowlatshahi D et al[38] conducted a prospective study of OAC-ICH patients treated with prothrombin complex concentrates (PCCs): they confirmed the safety and efficacy of this reversal therapy, and highlighted that time to INR control and baseline ICH volume did not correlate with outcome. Lee SM et al[77] in their observational retrospective study on primary ICH, identified 5.6% of cases of

ICH as being correlated with warfarin. OAC-ICH patients were older and OAC-ICH was correlated with location (lobar versus deep), larger haematoma volumes and a higher rate of haematoma expansion. INR values correlated with haematoma volume but not with haematoma expansion. Regarding OAC-ICH outcome, Zubkov AY et al[158] conducted a retrospective outcome study in 88 patients with OAC-ICH (defined as an ICH occurring in a patient treated with OAC at the time of ICH and with an INR $\geq$ 1.5), finding that a lower level of GCS scale at presentation and a larger initial ICH volume predicted poor prognosis in OAC-ICH patients. There was a trend towards a correlation between haematoma expansion and poor outcome, while no correlations were found between INR values or time to INR correction and HE or outcome.

- **lipid profile and hypercholesterolemia**: although a definite conclusion has not yet been reached, an inverse association has been hypothesized between total cholesterol and LDL cholesterol level and risk of haemorrhagic stroke[145]. In a study investigating the relationship between low LDL levels and ICH, a total cholesterol level of < 150 mg/dl in the presence of active statin use was associated with greater haemorrhage volume and worse outcome compared to statin users with higher cholesterol[91]. Another study found that LDL cholesterol levels < 95 mg/dl were associated with increased haemorrhagic growth without significant difference in pre-ICH statin exposure (Rodriguez-Luna D et al. Serum low-density lipoprotein cholesterol level predicts hematoma growth and clinical outcome after acute intracerebral hemarrhage. JCereb Circ 2011 42: 2447-2452). Conversely, the study by Pletsch et al evaluated the relationship between daily alcohol use, LDL and haematoma expansion: this study suggested that neither chronic daily alcohol use nor a low LDL level in combination with daily alcohol use can be used to predict ICH growth. A low LDL level in combination with daily alcohol use may be linked to larger, more severe ICH but the study could not demonstrate a relationship with haematoma expansion or poor clinical outcome[107]. Moreover, a recent study on 1093 ICH patients did not evidence a relationship between statin consumption and haematoma growth, while a continued or a new statin use after ICH could improve 3-month disability[126]. A decline in serum total cholesterol and LDL levels before primary ICH has recently been shown, independently of statin or alcohol

use[105] and these changes have been proposed to have a role in precipitating the occurrence of ICH. It has been proposed that APOE genotype (APOE e4 carriers) may influence these temporal lipid trends in ICH and this effect differs from APOE associations with steady-state serum lipid levels[106,117]. APOE e2 and e4 have been demonstrated to increase the risk of ICH in lobar regions, while APO e4 is independently associated with increased risk and recurrence of nonlobar ICH, presumably through nonamyloid-related mechanisms, and this could be through the effect on serum lipids (with a decreasing detrimental effect of e4 as serum LDL levels increase)[117]. From a pathogenetic point of view, the role of LDL in vessel fragility and clot stabilization needs to be further explored before concluding that a low LDL level confers risk of bleeding. This association has been hypothesized to be the result of loss in vascular integrity in low circulating cholesterol states, which predisposes toward vessel rupture in ICH, although the complex role of lipids in cellular biology, inflammation, and signalling, in addition to cell membrane integrity, makes it difficult to attribute the observed associations to any one mechanism[105,106]. Low cholesterol may play a role in promoting smooth muscle cell necrosis of the arterial medial layer; the impaired endothelium appears to be more susceptible to microaneurysms, which were the chief pathological finding of ICH, thereby contributing to the onset of haemorrhage. High-density lipoprotein cholesterol level seems to be positively associated with risk of intracerebral haemorrhage[144,145] and recent studies have suggested an association between genetic variants of CETP (cholesteryl ester transfer protein) and the risk of ICH, as opposed to their effect on the risk of cardiovascular events[4].

- **history of hypertension and elevated BP values:** a significant association has been demonstrated between high maximum systolic blood pressure (SBP) between baseline and second CT scans and the occurrence of haematoma expansion. Analysis of target SBP indicated that haematoma enlargement occurred more often in patients with a target SBP of ≥ 160 mmHg[68,100]. The problem of hypertension, elevated BP values and ICH is complex and is still the object of debate (see chapter *Blood pressure management in acute ICH* for more details).

- **history of diabetes mellitus and hyperglycaemia** that may result from a history of diabetes or a

stress reaction to ICH. The presence of a significant causative relationship between diabetes mellitus and primary intracerebral haemorrhage has not been confirmed and to date diabetes mellitus cannot definitely be considered an independent risk factor for ICH1[4,58]. However, elevated serum glucose on presentation has been associated with perihaematomal oedema, cell death, haematoma expansion, and poor clinical outcomes in ICH, although not all studies agree on this[11,16,68,123,131,133,158]. Moreover, a decline in serum glucose concentration could correlate with a reduction in the proportion of subjects with haematoma expansion and poor clinical outcome1[12]. To date it is not clear whether higher glucose at presentation could be a consequence of severe neurological injury or actually independently contributes to it: possible mechanisms are thought to be increased induction of inflammatory interleukins (TNF-a and IL-1) with increased permeability of the blood brain barrier, perihaematomal oedema and cell death, and the increased production of kallikrein which inhibits platelet aggregation.

- **obesity**: as a precursor of several predisposing conditions (including hypertension and diabetes mellitus), obesity might be involved in the biological mechanisms of brain haemorrhage but a recent meta-analysis of prospective studies, in addition to data from a large Chinese population cohort documented no independent effect of obesity on the rate of ICH[130,140]. Moreover, a subsequent study by Pezzini et al reported that obesity increased the risk of deep ICH, mostly through an indirect effect on hypertension and other intermediate obesity-related comorbidities, but had no major influence on the risk of lobar ICH[104].

- a**etiological subtype**: structural, medication, systemic and hypertensive ICH (according to the SMASH-U classification) seem to be the aetiological subtypes associated with a higher risk of significant HE compared with amyloid ICH patients[22].

- **smoking:** the association between tobacco use and ischemic stroke is not surprising. Cigarette smoking has been linked to both small and large vessel atherosclerotic disease and has been extensively studied in both the cerebrovascular and the cardiovascular literature. Although the effect of smoking on ICH has been less extensively studied, a correlation has been proposed

between cigarette smoking and ICH: a study by Gill et al highlighted that the relative risks of cigarette smokers compared with nonsmokers for subarachnoid haemorrhage, intracerebral haemorrhage, and cerebral infarction, after adjustment for the possible confounding variables, were 4.5, 1.8, and 3.2 for men and 2.5, 1.3, and 2.3 for women, respectively[49]. On secondary analysis, the effect appeared to be dose-dependent: any history of smoking OR 1.84 of smoking over ICH (CI 1.19-2.84); current use OR 2.23 of smoking over ICH (CI 1.37-3.62), heavy use OR 2.48 of smoking over ICH (CI 1.5-4.13). The dose-response relationship observed with tobacco abuse can be explained because heavier, more frequent use amplifies vessel narrowing, with rupture6[7,72]. Moreover, smoking causes structural damage to the arterial wall which can increase the possibility of continuous bleeding after ICH[150]: a statistically significant correlation has been observed between smoking and haematoma expansion and current smoking has been included in the recent HEP score proposed to predict the probability of haematoma expansion.

1.4.2 Radiological predictors of haematoma expansion:

Proposed radiological predictors of haematoma expansion are:

- **shorter time to first CT scan** (<6h vs>6h)[68,81], as early presentation may identify those patients early in the course of their disease, when bleeding is ongoing.

- **haematoma location**: in the ICH score, a grading scale for predicting ICH outcome, ICH location has been categorized as infra or supratentorial, and infratentorial location has been demonstrated to be a significant independent predictor of 30-day mortality[56]. In the same study, location, defined as deep, lobar, cerebellum or brainstem, has not been demonstrated to correlate with clinical outcome, and other studies have confirmed this result[18,22]. Involvement of the inferior parietal lobule, posterior insula and posterolateral thalamus are related to a poor prognosis, probably because the involvement of these sites could contribute to impairment of autonomic blood pressure regulation. Intraventricular haemorrhage extension, suggested to be a predictor of poor functional outcome, is correlated with the primary location of ICH, and thalamic and caudate locations have the highest

intraventricular expansion frequency. Cerebellar ICH seems to have the best prognosis whereas brainstem ICH the most lethal[41].

- **baseline ICH Volume**: ICH volume has classically been divided into 3 groups representing small (< 30 cm3), medium (> 30 < 60 cm3), and large haematoma size (> 60 cm3). Several studies have suggested that medium and large haematomas at all locations (> 30 mL) are associated with poor functional outcomes[8,15] and on this basis, baseline ICH volume has been included in important clinical grading scales that allow risk stratification in patients with ICH at presentation[56,81]. While ICH volume is a component of the ICH Score, its association with outcome is not as strong as the other predictors. ICH volume does not in fact seem to be an independent predictor of outcome in infratentorial haemorrhages (small haemorrhages in the brainstem or cerebellum may have catastrophic consequences, making location rather than size the more important predictor of infratentorial ICH). Moreover, patients with larger haematomas who died also present other predictors, such as low GCS score, advanced age, or IVH which influenced outcome to a greater degree. Baseline haematoma volume has also been associated with haematoma expansion and is included in two algorithms to predict haematoma growth[18,36,146].

-**intraventricular haemorrhage**: several studies have suggested that intraventricular haemorrhage is associated with poor functional outcomes leading to the inclusion of intraventricular haematoma expansion in an important clinical grading scale that allows risk stratification in patients with ICH at presentation[8,56]. Other studies have investigated the association between intraventricular hemorrhage and haematoma expansion: in a study of 627 patients, Fujii et al. reported that intraventricular haemorrhage did not predict haematoma expansion in patients with spontaneous ICH[47]. In another study of 183 patients, Silva and colleagues observed that intraventricular bleeding is associated with early ICH growth[125]. Li et al collected a total of 160 patients with ICH: multivariate analyses demonstrated that at a short time from onset to baseline CT scan, the initial haematoma volume and the presence of intraventricular haemorrhage on follow-up CT scan were independently associated with haematoma enlargement[81]. These results have been included in the

development of clinical-radiological scores to predict the risk of haematoma growth[146].

- **the spot sign**: in primary ICH the presence of contrast extravasation after computed tomographic angiography (CTA), termed spot sign, predicts haematoma expansion and mortality with a sensitivity of 51% and specificity of 85%[154]. Spot sign is defined according to four criteria: 1) serpiginous or spot- like appearance within the margin of a parenchymal haematoma without connection to an outside vessel; 2) contrast density greater than 1.5 mm in diameter in at least one dimension; 3) contrast density (hounsfield units HU) at least double that of the background haematoma; 4) no hyperdensity at the corresponding location on non-contrast CT[135]. The CTA spot sign occurs in about a third of patients scanned within 3 hours and on the basis of data from single-centre studies, the predictive value for substantial haematoma growth within 3 hours is high; specificity and positive predictive value decline with increasing time from onset but negative predictive value remains unchanged. But the biological underpinnings of the spot sign are not fully understood: does it represents active contrast extravasation and is therefore a visual manifestation of continued bleeding? (other hypotheses are microdissection? Charcot Bouchard aneurysms? pseudoaneursyms?). The PREDICT study (predicting haematoma growth and outcome in intracerebral haemorrhage using contrast bolus CT)[33] is a multicentre prospective observational cohort study which recruited patients with ICH smaller than 100 ml, presenting at less than 6 hours from symptoms onset. ICH expansion, defined as absolute growth greater than 6 ml or relative growth of more than 33% from initial CT. The primary aim was to validate previous single-centre observations in a prospective multicentre study[51,70,80,102,138]. Primary outcome was substantial haematoma expansion at follow-up CT scan; secondary outcomes included early neurological worsening, mRS score at three months and mortality at three months. It confirms that CTA spot sign is a predictor of haematoma expansion and is associated with poor prognosis, clinical worsening and mortality. The SPOT SIGN SCORE[32] predicts significant haematoma expansion, in particular considering spot sign numbers[62].

- **spot sign growth**[19]: the study by Brouwers and colleagues was thought to determine whether the size of the spot sign changed on delayed imaging, and if so, whether the rate of change predicted haematoma expansion and mortality beyond the simple presence of the spot sign (using a first-pass CTA for spot sign and volume measurements, a 90-second delayed CTA for repeated spot-sign reading and volumetric measurements). It enrolled 162 ICH patients, 21% presented haematoma expansion. In univariable analysis, baseline ICH volume, CTA spot sign and contrast extravasation rate were all associated with in-hospital mortality. In multivariable analysis (adjusted for sex, age and warfarin use), time to CTA, baseline ICH volume and contrast extravasation rate were all independently associated with in-hospital mortality (as well as with haematoma expansion, except for ICH volume but the sample size was small). Contrast extravasation rate was also associated with 90-day mortality and haematoma expansion. In conclusion: CTA contrast extravasation rate seems to predict haematoma expansion, in-hospital mortality and 90-day mortality in primary ICH patients, suggesting that spot sign represents active bleeding and may additionally help to better select patients at high risk. The presence of an increasing number of spot signs on delayed CTA provides additional evidence for the avalanche expansion model of cascading small vessel injury proposed by Fisher.

- **haematoma density and shape** are thought to be associated with haematoma expansion[10,13,30]. In particular,

- **the blend sign** characterises a hematoma with a hyperdense and a hypodense area. Specifically, it is defined as a blending of a relatively hypoattenuating area with an adjacent hyperattenuating region within a haematoma; there is a well-defined margin between the hypoattenuating area and adjacent hyperattenuating region which can be easily recognized by the naked eye; the haematoma should have at least a 18 Hounsfield-unit difference between the two density regions; the relatively hypoattenuating area was not encapsulated by the hyperattenuating region. It is obtainable in noncontrast computed tomography at admission, shows a high correlation with the CTA spot sign and, when present (20% of cases), seems to be a reliable predictor of secondary neurological

deterioration after spontaneous intracerebral haemorrhage[82,127].

- **fluid-blood levels** are thought to be associated with underlying coagulopathy[60,64] and are associated with haematoma expansion at 24 hours1[3].

1.5 Perihaematomal oedema:

Perihematomal edema (PHE) is the radiological manifestation of secondary injury to brain parenchyma that occurs after the initial injury caused by mechanical tissue disruption and the mass effect of the haematoma. It is a combination of cytotoxic oedema and vasogenic oedema: brain oedema increases in the first 24 h progressively and increases rapidly 3 days after onset, reaches its initial peak at the 4th or the 5th day and remains elevated until 9–14 days and then decreases[153].

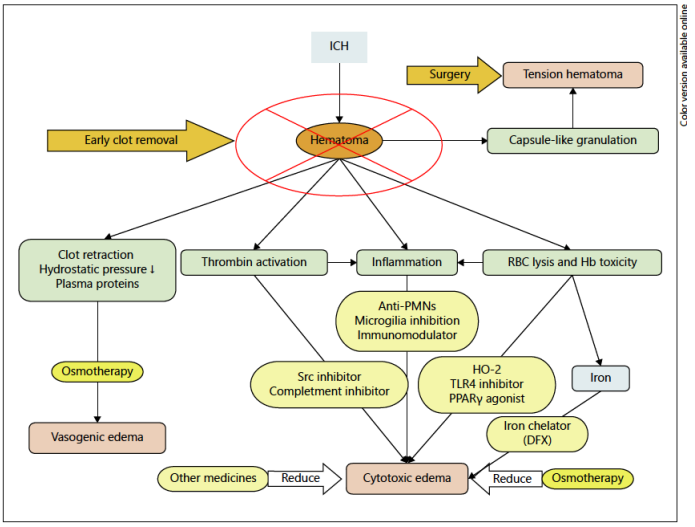

Fig 2: Mechanisms of oedema development in ICH and treatment (from Zheng H et al. Mechanism and therapy of brain oedema after intracerebral haemorrhage. Cerebrovasc Dis 2016; 42: 155-169)

In particular in the very early phase (first few hours) hydrostatic pressure and clot retraction develop, with the extrusion of serum from the haematoma into the surrounding tissue. A second phase (first few days) is related to the coagulation cascade and thrombin production causing inflammation, oedema by disruption of the blood brain barrier and neuronal injury mediated by the complement cascade, TNFa and metalloproteinases (cytotoxic oedema). Factors released from activated platelets increase vascular permeability, and the third phase is related to erytrocyte lysis

and haemoglobin toxicity[128,153]. Thrombin cascade and erythrocyte lysis products can aggravate vasogenic oedema, while oxidative stress induced by vasogenic oedema and the release of cytotoxic substances could induce cytotoxic oedema. Hence, vasogenic oedema and cytotoxic oedema interact with each other and lead to a vicious circle. Compared with spontaneous ICHs (SICHs), clinical tests have shown that thrombolysis-related ICHs have both lower absolute and relative oedema, indicating that intrahaematomal blood clotting is a reasonable factor for the formation of hyperacute PHE[48]. The degree of cerebral oedema and its growth are strongly related to the size of the underlying haematoma and there is still controversy as to whether PHE has an independent effect in determining outcome in ICH patients[5,128]. A recent study by Murthy enrolled 596 ICH patients (haematoma expansion in 122, 34.9%). PHE expansion has been significantly associated with poor functional outcome after ICH with a location-dependent and a volume-dependent effect (small-to- moderate volume haematoma and basal ganglia ICH)[95].

1.6 Intraventricular extension:

Intraventricular extension may occur simultaneously with ICH or within 24-72 hours after onset (see above for more details).

1.7 Inflammation:

It has been reported that a white blood cell count above 10,000/ml3 within the first 72 hours of hospital admission, a body temperature of above 37.5°C, or an increased neutrophilic count are associated with deterioration[79,132]. The inflammation response predicts a worse short-term and long-term outcome: it has been demonstrated that inflammatory response took place in and around the haematoma after ICH with the infiltration of neutrophils and macrophages and activation of microglia[52]. Inflammation can cause cell swelling and blood brain barrier disruption, and then causes brain oedema. Activated microglia and infiltrating leukocytes release cytotoxic mediators contributing to secondary injury. Clinical studies have proven that erythrocytes infiltrate into the

brain immediately, along with leukocytes from peripheral blood, macrophages and plasma proteins[142], and animal experiments have shown that CD4+ T lymphocytes were the main cause of brain leukocyte infiltration. But within 12 h after onset of ICH, inflammatory macrophages and dendritic cells comprise the majority of infiltrating leukocytes. Neutrophils or polymorphonuclear leukocytes (PMNs) are the first leukocytes to infiltrate the nervous system within 4–5 h after ICH, and reach a peak value at 3 days. PMNs may cause direct neurotoxicity to the ICH brain by releasing matrix metalloproteinases (MMPs), reactive oxygen species (ROS), and tumour necrosis factor-alpha (TNF-alpha) or other cytokines. Leukocytes exist only for about 2 days after infiltrating into the haemorrhagic brain, but it can cause further damage by stimulating microglia and macrophages[94].

1.8 Developing ICH or HE prediction scores:

Several studies in recent years have focused on deriving and validating prognostic scores for detecting early mortality after an ICH in the acute setting. In 2001, a simple clinical grading scale was been proposed that allows risk stratification on presentation of ICH patients[56].

The **ICH score** is the sum of individual points assigned as follows: GCS score 3 to 4 = 2 points, 5 to 12 = 1 point, 13 to 15 0 points; age ≥ 80 years yes = 1 point, no =0 points; infratentorial origin yes =1 point, no =0 points; ICH volume ≥ 30 cm^3 = 1, <30 cm^3 =0; intraventricular haemorrhage yes =1 point, no = 0 points.

Score 0 risk of 30-day mortality 0%

score 1 risk of 30-day mortality 13%

score 2 risk of 30-day mortality 26%

score 3 risk of 30-day mortality 72%

score 4 risk of 30-day mortality 97%

score 5 risk of 30-day mortality 100%

Some prediction scores for haematoma growth have also been developed.

A 9-point score for predicting haematoma expansion[18]**:** In this study, 817 patients with primary ICH were enrolled. Haematoma expansion was defined as a haematoma growth of more than 6 ml or 33%. The ICH location was categorized as deep, lobar, cerebellar or brainstem. Haematoma expansion was present in 156 patients (19.1%). In multivariable analysis predictors of expansion were: warfarin use, the CTA spot sign, shorter time to CT (≤ 6h vs > 6h) and baseline ICH volume (< 30, 30-60 and > 60 ml). A 9-point prediction score was derived based on regression estimates and was subsequently tested in the independent validation cohort.

Table 3. Individual Components of the Prediction Score for Hematoma Expansion

Variable	Points
Warfarin sodium use	
No	0
Yes	2
Time to initial CT, h	
≤6	2
>6	0
Baseline ICH volume, mL	
<30	0
30-60	1
>60	2
CT angiography spot sign	
Absent	0
Present	3
Unavailable	1
Total	0-9

Abbreviations: CT, computed tomography; ICH, intracerebral hemorrhage.

Fig 3: A 9-point score for predicting haematoma expansion (by Brouwers HB, Chang Y, Falcone GJ, Cai X, Ayres AM, Battey TW, Vashkevich A, McNamara KA, Valant V, Schwab K, Orzell SC, Bresette LM, Feske SK, Rost NS, Romero JM, Viswanathan A, Chou SH, Greenberg SM; Rosand J, Goldstein JN. *Predicting hematoma expansion after primary intracerebral hemorrhage*. JAMA Neurol 2014; 71 (2): 158-164)

0 points → risk of haematoma expansion: 5.7%

1-3 points 1-3 → 12.4%

4 points and over (high risk) → 36.4% (Points > 7 → risk of haematoma expansion 46%, 9 points → risk of haematoma expansion 80%).

A 24-point BRAIN score for predicting haematoma expansion[63,146]: a 24-point score derived from INTERACT2 based on baseline ICH volume (mL <10 0 points, >10<20 5 points, > 20 7

points), recurrent ICH (yes= 4 points), anticoagulation with warfarin at symptoms onset (yes=6), intraventricular extension (yes=2), and number of hours to baseline CT from symptoms onset (<1 5 points, 1-2 4 points, 2-3 3 points, 3-4 2 points, 4-5 1 points, >5 0 points) predicted the probability of ICH growth.

0 points, risk of haematoma growth 3.4%

24 points, risk of haematoma growth 85.8%.

The Hematoma Expansion Prediction (HEP) Score[150] with 6 variables: time from ICH onset to baseline CT (<3 h No 0 Yes 3 points), diagnosis of dementia (No 0, Yes 4 points), current smoking (No 0, Yes 3 points), antiplatelet drug use (No 0, Yes 3 points), GCS score at presentation (3–5: 3 points; 6–8: 2 points, 9–11: 1 point, 12–15: 0 points), SAH at baseline CT (No 0, Yes 2 points). The total sum can vary from 0 to 18 points.

0 points: estimated risk of substantial haematoma expansion in the first 72 hours - 0.089

1 point: estimated risk of substantial haematoma expansion in the first 72 hours - 0.210

2 points: estimated risk of substantial haematoma expansion in the first 72 hours - 0.42

3 points: estimated risk of substantial haematoma expansion in the first 72 hours - 0.663

4 points: estimated risk of substantial haematoma expansion in the first 72 hours - 0.843

5 points: estimated risk of substantial haematoma expansion in the first 72 hours - 0.936

6 points: estimated risk of substantial haematoma expansion in the first 72 hours - 0.975

7 points: estimated risk of substantial haematoma expansion in the first 72 hours - 0.991

8 points: estimated risk of substantial haematoma expansion in the first 72 hours - 0.997

9 points: estimated risk of substantial haematoma expansion in the first 72 hours - 0.999

10 points: estimated risk of substantial haematoma expansion in the first 72 hours - 1.000

1.9 Medical management of intracerebral haemorrhage:

1.9.1 Blood pressure management in acute ICH:

Initial post-ICH BP is often much higher than the last pre-morbid level. Acute hypertensive response is common, often self-limiting, and may affect outcome in ICH[100,111,113]. In a portion of these patients, the underlying cause is often an undiagnosed or inadequately treated hypertension that has been unmasked. However, elevation and spontaneous reduction in the initial blood pressure during the next few days support the role of other transient and stroke-specific mechanisms:

1) the Cushing response to the mass effect of cerebral oedema due to stroke with consequent increased intracranial pressure (ICP), particularly in the presence of brainstem compression.

2) the shifting of the cerebral autoregulatory mechanisms to a higher level in patients with a history of chronic hypertension. With increasing BP, there is progressive vasoconstriction of arterioles until the BP exceeds the upper limit of autoregulation, followed by breakthrough vasodilation, increase in cerebral blood flow, blood-brain barrier dysfunction, and cerebral oedema. In chronic hypertension, the lower end of the autoregulation curve is shifted toward high pressure, presumably because vessel wall thickening and luminal narrowing limit the capacity of the resistance vessels for dilation.

3) the neuroendocrine response, with activation of the sympathetic nervous system and the renin-angiotensin axis, has also been implicated in the development of hypertension in acute stroke. The parasympathetic and sympathetic nervous systems are lateralized to the left and right cerebral hemispheres, respectively. Prefrontal and insular cortices provide inhibitory and excitatory input, respectively, through pathways that connect to the nuclei in the brainstem, particularly in the nucleus tractus solitarius and ventrolateral medulla. Further modulation is provided by the cingulated cortex, amygdala, and hypothalamus. Because of the widespread distribution of these areas, most stroke lesions involve these areas to a varied extent (most notably, intraventricular haemorrhage including the third or fourth ventricle or ICH with insular involvement are reported to have lower baroflex sensitivity). Increased sympathoadrenal tone with subsequent release of renin and vasoconstriction of arterioles results from direct injury to inhibitory or modulatory brain regions or from indirect effects of reduced parasympathetic activity, leading to impaired cardiac

baroreceptor sensitivity in patients with stroke. Although direct injury is the most likely explanation, an indirect effect of muscle paralysis or the release of neurotransmitters such as nitric oxide during ischemia, may be contributing factors to altered activity of these nuclei.

4) other stress responses to hospitalization, pain, urinary retention, or concomitant infection may lead to abnormal autonomic activity and raised levels of circulating catecholamines and inflammatory cytokines, and may subsequently contribute to the hypertensive response. Presumably, these abnormal autonomic responses normalize over a few hours owing to spontaneous or therapeutic recanalization and resolution of the ischemia and perhaps due to other neural compensatory mechanisms.

Blood pressure lowering after ICH is intuitively attractive as a means to prevent continued bleeding or perihaematomal oedema: an observational study suggested that more aggressive SBP reduction may have greater benefit in reducing the rate of haematoma expansion. The rate of haematoma expansion was 9% in patients with SBP< 150 mmHg and 30% among patients treated to maintain SBP < 160 mmHg or a higher threshold[100]. On the other hand, the theoretical concerns of lowering blood pressure refer to the potential reduction of cerebral perfusion with the concomitant risk of ischemia, as cerebral autoregulation may be impaired in acute intracerebral haemorrhage and in chronic hypertension with the potential for worsening ischaemia in the perihaematomal region. This hypothesis has not been confirmed: recent studies suggest that a reduction in BP may be tolerated because of the presence of reduced metabolism and not ischaemia in the perihaemorrhagic area, and of preserved autoregulation[20,53,109]. Unfortunately, randomised studies do not as yet provide sufficient evidence to support a specific blood pressure target.

INTERACT trial was a randomized controlled trial that enrolled 404 patients with CT-confirmed ICH, elevated systolic blood pressure (SBP) (150 to 220 mmHg) and capacity to start BP lowering within 6 hours from ICH onset[2,3,6]. Patients were randomly assigned to receive early, intensive management of SBP (target SBP 140 mmHg within 1 hour from randomisation and to mantain the

target for the next 7 days) using routine intravenous agents or standard guideline-based pressure control (SBP< 180 mmHg). Baseline and repeat CTs (24 and 72 hours) were performed. Results:

1) early intensive BP lowering is clinically feasible and well tolerated.

2) intensive group showed significantly lower mean proportional haematoma growth at 24 h, but this difference was not significant after adjustment for initial haematoma volume and time from ICH onset to CT. Substantial haematoma growth (defined as haematoma growth of > =33% or >= 12.5 mL) was smaller in the intensive group (36% lower) but not significantly so.

3) early intensive BP-lowering treatment attenuated haematoma growth over 72 hours in ICH, but there were no appreciable effects on perihematomal oedema.

3) reductions in proportional haematoma growth produced by randomized intensive blood pressure-lowering treatment over 72 hours decreased progressively with delays in initiation of treatment.

4) patients with an initial SBP >= 181 mmHg seemed to have the greatest benefit from intensive SBP reduction.

INTERACT 2 showed a borderline significant effect on reducing the rate of the primary outcome – death and severe disability (defined as a score of 3 to 6 on the modified Rankin scale [mRs]) at 90 days, across a wide range of baseline SBP levels, and the target SBP level of 130-139 mmHg likely provides the maximum benefit in acute ICH. No significant reduction of haematoma expansion was observed.

A viable explanation for these results is the indiscriminate enrolment of unselected patients with ICH (i.e. 41% of INTERACT II participants underwent randomization 4 or more hours after symptoms onset and it is reasonable to assume that many of these haematomas were already stable; more than 50% of the patients underwent randomization with an initial SBP of less of 180 mmHg; primary treatment failure was seen in 66% of participants within 1 hour after randomization) resulting in a low rate of significant haematoma expansion. A key issue is likely to be time. Phase 2 or 3 clinical trials enrolled patients solely based on early presentation – 3 or 6 hours from onset (early presentation as a surrogate for haematoma expansion).

ATACH (Antihypertensive treatment of acute cerebral haemorrhage): an open-labelled pilot study involving a 3-dose-tiered trial of reducing SBP to predetermined levels: 170-200, 140-170, 110-140 mmHg in 60 subjects with supratentorial ICH within 6 hours of symptoms onset. It showed that aggressive SBP reduction to 110-140 mmHg in the first 24 hours using intravenous nicradipine was well tolerated with a low risk of haematoma expansion, neurological deterioration and in-hospital mortality[110].

ATACH II randomized, multicentre, two-group, open-label trial to determine the relative efficacy of intensive versus standard antihypertensive treatment that was initiated within 4.5 hours after symptom onset and continued for the next 24 hours in patients with spontaneous supratentorial intracerebral haemorrhage. Eligible patients were randomly assigned to a systolic blood-pressure target of 110 to 139 mmHg or a target of 140 to 179 mmHg using intravenous nicardipine. The intensive treatment to achieve a target SBP of 110 to 139 mmHg did not result in a lower rate of death or disability than the standard reduction to a target of 140 to 179 mmHg[114]. On the basis of these studies, ESO guidelines 2014 and Italian SPREAD guidelines of 2016[65] suggest the rapid reduction of SBP < 140 mmHg in acute ICH (within 1 hour and prolonged for 7 days).

1.9.2 Acute haemostatic therapy and coagulopathy reversal:

Prolonged haematoma expansion attributed to anticoagulation-associated ICH provides a pathophysiological rationale for rapid haemostatic treatment and conceptually ultra-early haemostatic therapy can be viewed as the emergency department counterpart to tissue plasminogen activator for acute ischaemic stroke. Randomised experimental studies suggest that the rapid reversal of anticoagulation in acute ICH could prevent extensive haematoma formation and improve functional outcome. Treatment options for anticoagulation reversal include vitamin K, fresh frozen plasma, prothrombin complex concentrate (PCC) and recombinant factor VIIa. The results of recent studies suggest that prothrombin complex concentrate corrects increased INR values more rapidly than fresh frozen plasma, whereas recombinant factor VIIa corrects INR values more reliably than

PCC[17,54,59,129]. Recombinant activated factor VII was developed for the treatment of spontaneous and surgical bleeding in patients with haemophilia A or B and inhibitors to factors VIII or IX, respectively. It binds to the surface of activated platelets where it generates activated factor X, enhancing local haemostasis after binding to exposed tissue factors. The relatively low frequency of systemic activation of coagulation associated with rFVIIa use, its rapid action at the site of bleeding and short half-life of 2.5 hours, suggest that rFVIIa may be an ideal agent for use during the earliest stages of ICH. The Recombinant Factor VIIa for Acute Intracerebral Haemorrhage phase IIB and phase III trials are randomized, placebo-controlled, dose-ranging studies testing rFVIIa in non-coagulopathic spontaneous ICH patients. The main object was to determine whether rFVIIa could limit ongoing bleeding and effectively reduce haematoma growth in acute ICH, and thereby improve outcome. The studies compared the efficacy of 3 different doses of rFVIIa (40, 80 and 160microg/Kg) to placebo, administered intravenously over 1 to 2 minutes. They both showed that rFVIIa reduced haematoma growth compared to placebo, especially at an increased dose and when administered within 3 hours of symptoms onset (the mean percentage increase in ICH volume was 34% in the placebo group compared with 13% for rFVIIa-treated patients, p 0.004. The absolute increase in ICH volume was 10.7 mL for placebo and 4.4 mL for rFVIIa-treated patients, p 0.009). Haematoma growth decreased but did not reduce mortality or improve functional outcome[85,86]. Moreover, recombinant Factor VIIa has been associated with relatively high-thrombosis rate (12.8-24%), likely due to the pro-coagulant state and thrombin burst associated with higher doses. In addition, even though recombinant FVIIa can lower the INR quickly, the INR is particularly sensitive to factor VII levels and INR correction may occur despite inadequate levels of factor II, IX and X that are required for haemostasis. Taking all these factors into account, current guidelines recommend against rFVIIa use in ICH and suggest administering PCC rather than fresh frozen plasma to patients with warfarin-associated ICH and INR >1.4 (4-factor PCC over 3-factor PCC)[46].

1.9.3 Osmotic therapy for cerebral oedema in ICH:

Increasing evidence suggests that PHE is independently associated with poor outcome and targeted oedema treatment strategies have been investigated. The space-occupying effect of haematoma, perihaematomal oedema and obstructive hydrocephalus can produce an increase in intracranial pressure (ICP): as intracerebral volume expands, ICP increases at a greater than linear rate, approximating an exponential function. Clinical signs only approximately reflect the level of ICP: except for headache, vomiting, and papilloedema, the signs of an intracranial mass are due to secondary tissue shifts induced by the mass, and not to raised ICP. Various modalities of treatment for ICP exist, including elevation of the head-end of the bed, osmotic therapy, barbiturate coma, analgesia and sedation, hyperventilation and CSF drainage[75]. Osmotherapy with mannitol or hypertonic saline is often applied in the acute phase of ICH to control the increased intracranial pressure. These agents can be given in various solutions as boluses for rapid ICP reduction or, in the case of hypertonic saline, as a continuous infusion to mitigate oedema formation, although there is a relative paucity of data on the comparative efficacy of various administration strategies[119]. The rapid effects of bolus therapy are well supported, and mannitol has been shown to work in a dose- and location-dependent manner, with the greatest ICP reductions in patients with supratentorial haemorrhages[75]. Although the short-term effects of mannitol and hypertonic saline are well established, their ultimate effects on clinical outcome are unclear. Recent studies and the Cochrane systemic review did not find significant differences in mortality and morbidity between treatment groups and controls[12,90,147]. Interestingly, a trend toward better outcomes in those with larger hematoma volumes was seen, suggesting that there may still be a relevant therapeutic effect on the outcome in certain patient populations.

1.9.4 Surgical Therapy:

Whether surgery is beneficial for patients with early haemorragic stroke is still controversia[l25]. Theoretically, early removal of the haematoma would not only relieve the mass effect from the clot, but, considering that the clot and thrombin are the primary predisposing factors of perihematomal

edema development, it would also reduce PHE development and other secondary brain injury processes[71]. Brain damage induced by ICH can be divided into primary injury (mainly the result of mechanical damage associated with the mass effect, which is related to hematoma volume) and secondary injury mainly due to PHE[155]. In the case of haematoma volumes <60 ml, secondary brain injury has been reported to be the dominant injury mechanism in the pathological mechanism of the ICH. Consequently, removal of the haematoma in the acute phase of larger hematomas is supposed to be effective in improving outcome of ICH patients, especially for hematomas <60 mL. Initially, haematoma reduction was conceived as surgical evacuation of the blood clot in its entirety (craniotomy and decompressive craniectomy with or without haematoma evacuation). However, 2 large-scale randomized controlled trials of early surgical evacuation have failed to demonstrate an overall improvement in outcomes in the surgically treated arm[88,89,143]. One large multicentre trial, the International Surgical Trial in Intracerebral Haemorrhage (STICH), included 1033 patients over an 8-year period to compare early surgery (within 96 hours of the onset of the haemorrhage) with medical therapy. The surgical procedure in 75% cases involved craniotomy and in the remaining cases less invasive procedures were used. The primary outcomes included death and disability at 6 months. The results of the study showed no benefit of early surgery over medical therapy in supratentorial ICH[88,89]. However the results should be interpreted with caution: the study excluded patients considered not to benefit from surgery and did not explore the results of certain types of surgery[134]. Moreover, the trial does not address the effectiveness of very early surgery in the first 12 hours after ICH onset, 26% of patients originally randomised to conservative treatment underwent surgery because of a worsening clinical condition, the design did not account for intraventricular haemorrhage and hydrocephalus, there was a low recruitment rate per centre, and standard craniotomy was used by the majority of surgeons. The subgroup analysis showed a possible non-significant benefit in patients with superficial lobar clots (within 1 cm from the cortex with GCS >8): the data suggested that certain subgroups (patients with cerebellar haematomas or superficial haematomas and a Glasgow Coma Scale of 9-12) may benefit from surgery. Given the failure of

traditional surgical methods to significantly improve outcomes in ICH, other surgical methods to try and reduce hematoma volume have been developed. Minimally invasive surgery (MIS) is the most promising of these, and trials are ongoing to determine its effectiveness[71]. The purpose of MIS is functional recovery, not life saving, by achieving a gross reduction in haematoma volume but not necessarily removing the entire blood clot. In addition to reduced trauma to the surrounding parenchyma, MIS has several other advantages when compared with open surgery: less blood loss, shorter operative times, and decreased exposure to general anaesthesia. There are multiple techniques for reducing haematoma volume through minimally invasive means: neuroendoscopic (NE) surgery, stereotactic haematoma aspiration, surgical aspiration in conjunction with the administration of fibronolytic agents. Mould et al conducted the Minimally Invasive Surgery and rtPA in ICH evacuation (MISTI) trial to evaluate the effectiveness of the clot lysis method[92]: the results showed that both haematoma volume and perihaematomal oedema were lower in the treatment group. A meta analysis by Zhou et al involving 12 high-quality randomised, controlled trials concluded that minimally invasive surgery (especially stereotactic aspiration) could significantly reduce the early mortality of patients with ICH and that those with a superficial haematoma between 25 and 40 ml were most likely to benefit from such approach[157]. In a recent work by Zhihong L et al[155] comparing minimally invasive puncture and drainage (MIPD) with endoscopic surgery (ES) in basal ganglia haemorrhage, the inclusion criteria included haematoma volumes ≥ 30 ml, preoperative GCS score >=4, age ≤ 75 years and no serious coagulation disorders. The study showed that ES evacuated haematoma more quickly than MIPD, while MIPD was less invasive than ES (less perihematomal oedema, anaesthetia time and blood loss). The authors suggested that MIPD might be more effective than ES in achieving better functional independence in patients with a haematoma volume of 30-60 mL or a GCS score of 9-14.

When intracerebral haemorrhage is complicated by intraventricular expansion the prognosis is worse. Naff et al tried removing the intraventricular clot with catheter-delivered rtPA in the Clot Lysis Evaluating Accelerated Resolution of IVH (CLEAR-IVH) trial: the results showed a lower

mortality rate in the treatment group[96]. The CLEAR III trial[55] is a randomised, double-blind, placebo-controlled trial which tested whether intraventricular boluses of alteplase through ventriculostomy catheters could improve outcomes in patients with intraventricular haemorrhage, routinely placing an extraventricular drain. The results were neutral: the proportion of patients treated with alteplase who achieved good functional outcome at 6 months was similar to that of patients in the control group, mortality was 11% lower in the alteplase group but at the cost of an 8% increase in the rate of survivors with severe disabilities. Greater intraventricular clot removal was, however, associated with improved functional outcomes (in the CLEAR III trial only 30% of the alteplase group reached the goal of 80% clot reduction), thus confirming that the premise of the trial was sound: effective clearance of intraventricular haemorrhage could improve functional outcome and mortality[115]. The recent work by Yuqian L and colleagues[152] demonstrated the superiority of endoscopic surgery and stereotactic aspiration over craniectomy in a population of 99 patients with supratentorial lobar ICH, especially in severe ICH (Volume > 60 ml or GCS 4-8).

To conclude, current practice and guidance from AHA[57] and ESO favour intervention in the following situations:

- superficial haemorrhage, GCS 9-12, volume 20-80 mL and/or deteriorating
- clot volume between 20 and 80 mls
- worsening neurological status
- relatively young patients
- haemorrhage causing midline shift/raised ICP
- cerebellar haematomas > 3 cm and/or causing hydrocephalus
- putaminal haematomas with GCS 9-12, volume 20-60 deteriorating.

A clearer definition of the best surgical approach in ICH patients is needed.

What we can say after this literature review is that intracerebral haemorrhage is still a scarcely understand pathology and current medical and/or surgical treatment does not seem to be a

determinant in improving ICH patient outcome. Studying haematoma expansion phenomenon could be a good starting point.

2. AIMS

The object of our study are intracerebral haemorrhages, both spontaneous and anticoagulant-related. The primary aim was to analyze the haematoma expansion phenomenon by researching possible HE-associated risk factors. The secondary aims were to evaluate ICH patient characteristics and outcomes, HE influence on outcome and to investigate any prognostic factors that could contribute to determining ICH outcome.

3. METHODS

We conducted an observational longitudinal study on retrospectively collected data of 206 consecutive patients with primary or anticoagulant-associated ICH who were admitted to the Stroke Units at the Neurology Unit of Treviso Hospital and Neurology Unit of St. Anthony's Hospital of Padova, from January 2011 to December 2015. Both Stroke Units have stroke specialists, with updated stroke pathway protocols and continuing stroke training. All patients were managed according to AHA/ASA stroke care guidelines for haemorrhagic strokes[57] which have not significantly modified over the past five years.

3.1 Patient selection:

We searched the electronic medical record system to identify all patients who had a discharge diagnosis of ICH (according to the International Classification of Diseases, ninth revision ICD-9, code 431). All patients with a diagnosis of ICH were screened for eligibility.

Inclusion Criteria:

- patients aged 18 years or older;

- patients presenting with symptomatic and radiologically confirmed ICH;

- patients diagnosed as having a primary ICH and/or an anticoagulant-associated ICH;

- patients who underwent an initial CT scan at the time of hospital admission (within 12 hours from symptoms onset) and a follow-up CT scan within 72 hours from baseline.

Exclusion criteria: patients having a secondary cause of ICH (including aneurysms, arteriovenous malformations, neoplasms, trauma, vasculitis, moyamoya disease, sinus venous thrombosis or haemorrhagic transformation of an ischaemic stroke), or patients not undergoing the second CT scan within 72 hours from the time of hospital admission were excluded from the study.

All patients included in our study underwent a neurosurgical evaluation at admission that excluded surgical treatment options.

3.2 Procedures:

We recorded baseline demographic characteristics and medical history (with particular regard to vascular risk factors): age, sex, history of hypertension (defined as blood pressure of >140/90 mmHg at least twice before stroke or already taking antihypertensive medications), history of diabetes mellitus (defined as glucose level >126 mg/dL preprandial on 2 examinations or glucose level >200 mg/dL postprandial before stroke, or as HbA1c >7.0%, or currently under hypoglycaemic treatment), current cigarette smoking (subjects were classified as current smokers if they were currently smoking ≥1 cigarettes per day on a regular basis), history of hyperlipidaemia (defined as total cholesterol concentration >200 mg/dL and/or triglyceride concentration >140 mg/dL the day after admission, or already under lipid lowering therapy), alcohol abuse (>300 g per week), obesity (body mass index >30 kg/m2), previous antiplatelet treatment (APT), previous anticoagulant treatment. Clinical presentation severity evaluated through the National Institutes of Health Stroke Scale (NIHSS) score at admission was also recorded. Clinical and haematological information obtained during hospitalization and included in our data collection were: fasting serum

glucose, fasting serum cholesterol (total, HDL and LDL), platelet count, International Normalized Ratio (INR), systolic and diastolic blood pressure (SBP and DBP) at admission. These variables were analyzed both as quantitative variables and categorized (blood glucose < or ≥ 160 mg/dl, total cholesterol < or ≥ 200 mg/dl, HDL cholesterol < or ≥ 40 mg/dl, LDL cholesterol < or ≥ 100 mg/dL, SBP < 140, 140-179 or ≥ 180 mmHg, DBP ≤ 120 or >120 mmHg, baseline haematoma volume ≤ 10, 11-29, ≥ 30 mL). The recorded follow-up data included outcome at 3 months and 1 year (evaluated with the modified Rankin scale mRs score), death, occurrence of new ischaemic or haemorrhagic strokes at 3 months and 1 year, possible institutionalization at three months and 1 year. The imaging findings considered were haemorrhage location (defined as lobar, deep, brainstem or cerebellar), presence of intraventricular extension, haematoma volume at baseline and at follow up. Haematoma volume has been calculated by using the ABC/2 method, derived from an approximation, according to the formula for ellipsoids. For the bedside *ABC*/2 method, the CT slice with the largest area of haemorrhage was identified. The largest diameter *(A)* of the haemorrhage on this slice was measured. The largest diameter 90° to *A* on the same slice was measured next *(B)*. Finally, the approximate number of slices on which the ICH was seen was calculated *(C)*. *C* was calculated by comparing each CT slice presenting haemorrhage with the CT slice with the largest haemorrhage on the same scan. If the area of haemorrhage for a particular slice was greater than 75% of the area on the slice where the haemorrhage was largest, the slice was considered to be one haemorrhage slice for the purposes of determining *C*. If the area was approximately 25% to 75% of the total area, the slice was considered to be half a haemorrhage slice; and if the area was less than 25% of the largest haemorrhage, the slice was not considered a haemorrhage slice. These CT haemorrhage slice values were then added together to determine the value of *C*. All measurements for *A* and *B* were made using the centimetre scale on the CT scan, to the nearest 0.5 cm. *A, B,* and *C* were then multiplied and the product divided by 2, yielding the volume of haemorrhage in cubic centimetres[73,61]. Given that the ABC/2 method can lead to imprecise assessments, especially for irregular shaped haematomas, we use the ABC/3 method for measuring haemorrhages without

ellipsoidal outlines[35]. The primary outcome was substantial haematoma expansion at follow-up CT scan, defined as absolute growth greater than 6 mL or relative growth of more than 33% from the initial CT[36]. Secondary outcomes were disability at follow up evaluated with the mRs score (3 months and 1 year), death (3 months and 1 year), occurrence of new cerebrovascular events at follow up (3 months and 1 year), and any institutionalization.

3.3 Statistical analyses:

We reported the results of quantitative variables as mean (standard deviation) or median (interquartile range); categorical variables results are reported as count and proportion in each category. In the univariate analysis searching for predictors of the outcomes considered, we compared quantitative variables with Student's t test, Mann-Whitney or Kruskal-Wallis test in the case of not normally distributed data. Categorical variables were analyzed with χ^2 or Fisher's exact test, when appropriate. The variables resulted statistically significant al the 10% in the univariate analysis were introduced in a multivariate logistic regression with backward stepwise selection method. For the binary outcomes (occurrence of a new cerebrovascular event, mortality and institutionalization at three months and 1 year) we used the binary logistic regression, for mRs (categorized as 0-2, 3-5, 6) at 3 months and 1 year we adopted an ordinal logistic regression model. The results of the logistic regression analyses are reported as odds ratio (OR) and 95% confidence interval (95% CI) and p-values. The multivariate analyses were conducted considering a 5% significance level.

The local Ethical Commitees approved the study.

4. RESULTS

A total of 206 patients fulfilled the inclusion criteria.

4.1 Characteristics of the study population:

For the characteristics of the study population see Table 1.

Demographic characteristics: all patients were of Caucasian ethnicity. 93 patients were females (45%), mean age was 74.6 years (SD 9.4). As regards the vascular risk factors, 165 patients suffered from hypertension (80%), 113 from hypercholesterolaemia (55%), 43 were diabetics (21%), 14 active smokers (8%), 29 were alcohol abusers (16%), and 31 were obese (27%). At the time of hospital admission for acute ICH, 68 patients were being treated with antiplatelet therapy (33%), 50 with anticoagulants (24%). Accordingly, in our population, 1/3 of ICH occurred during antiplatelet therapy and 1/4 during anticoagulation. In terms of sex differences in vascular risk factors, female patients were significantly older than males (p=0.0017), while men were more frequently alcohol abusers, active smokers and obese (p=0.0103, p=0.0021 and p=0.0393 respectively). No significant differences between sexes emerged in history of hypertension, diabetes mellitus, hyperlipidaemia or in previous antithrombotic therapy.

Haemorrhage characteristics: ICH location was deep in 107 patients (51.9%), lobar in 85 (41.3%), in the brainstem in 4 (1.9%) and cerebellar in 10 (4.9%). At presentation, 36 ICH patients had intraventricular extension (17.5%). Median haematoma volume was 6.3 mL (IQR 2-5-13.5), mean 9.97 mL (SD 11.03). Baseline haematoma volume in ICH patients with previous anticoagulant therapy was not significantly higher than in ICH patients with no previous therapy, and no significant sex or age-related differences emerged in the characteristics of the haemorrhage.

Admission data: at admission, mean SBP was 168 mmHg (SD 31) and mean DBP 89 mmHg (SD 18). At determination of the biochemical variables, median blood glucose level was 117 mg/dL (IQR 104-142), mean total cholesterol level was 190 mg/dl (SD 44), median HDL cholesterol was 52 mg/dL (IQR 42-65), median LDL cholesterol was 114 mg/dL (IQR 87-137); median INR was 1.0 (IQR 1.1-1.29) and median platelet count was 211 500 (IQR 178 000-256 000). Median NIHSS at admission for ICH patients was 8 (IQR 4-17), but scores did not significantly differ between the

sexes. 49 patients (23.7%) underwent reversal therapy (vitamin K antagonists+ fresh frozen plasma or vitamin k antagonists + prothrombin complex concentrate), i.e. all patients taking oral anticogulants with an admission INR >1.4 underwent reversal therapy.

Haematoma expansion: a total of 59 patients (28.6%) had substantial haematoma expansion at the 72 h follow-up CT scan.

Outcome: at three months from the index event, 153 patients underwent a reliable follow up. At 3 months' follow up 4 patients (2.6%) had suffered an ischaemic stroke, and 4 patients (2.6%) had suffered a new ICH. Median mRs at three months was 4 for females (IQR 3-6) and 4 for males (IQR 2-5); 38 patients (24.7%) were dead and 16 patients (10.5%) were institutionalized. At one year follow up, 138 of the 168 patients still alive underwent a reliable follow up. A total of 6 patients (4.4%) had suffered an ischaemic stroke one year after the ICH event, while a total of 8 patients (5.8%) had suffered a new ICH. Median mRs was 4 for female (IQR 3-6) and 4 for male patients (IQR 1-6); 50 patients had died (28.4%) and 24 patients (19.2%) had been institutionalized; 27% of ICH patients had an mRs 0-2 (independence). Overall, in our ICH population, at one year from the ICH event, occurrence of ischaemic stroke was 4.3%, recurrence of a new ICH was 5.8%, mortality was 28.4% and institutionalization 19.2%.

4.2 Predictors of significant haematoma expansion:

Table 1 reports the clinical characteristics of ICH patients with and without significant haematoma expansion. Our study highlighted a higher percentage of significant haematoma expansion in male compared to female patients (34% in males, 23% in females, p=0.0809) but no significant relationship emerged between haematoma expansion and anamnestic data such as age, history of hypertension, diabetes mellitus or hyperlipidaemia, current smoking, alcohol abuse, and obesity. No significant relationship emerged between haematoma expansion and previous antiplatelet treatment, or previous anticoagulant therapy or reversal therapy. No significant relationship was found between haematoma expansion and haemorrhage characteristics as location, baseline haematoma

volume and intraventricular invasion at presentation. No association were observed between haematological parameters or blood pressure values examined as continuous variables and haematoma expansion. A statistically significant association was found between clinical severity at presentation calculated by the NIHSS score and haematoma expansion (p=0.0010) (see Table 1). Moreover, NIHSS score correlated with baseline haematoma volume (Spearman's correlation coefficient 0.55528, p <0.0001) and with haematoma location (p=0.0005), with significant differences between lobar and deep location that shows the higher NIHSS values. In conclusion, considering the 10% level of significance, univariate analysis did not reveal a statistically significant difference between the two groups (significant haematoma expansion versus non-significant haematoma expansion) for these variables, except for NIHSS score and sex. Multivariate analysis confirmed sex and clinical severity at presentation as predictors of significant haematoma expansion: male patients were twice as likely as females to undergo haematoma expansion (OR=2.03, 95% CI: 1.05 ; 3.93), and the probability of HE increased 1.082 fold for each one-point increase in NIHSS score (OR= 1.08, 95% IC: 1.03 ; 1.13).

4.3 Predictors of outcome at three months:

For associations between variables and outcome see Table 2.

Demographic characteristics: no associations were observed between demographic characteristics and 3-month occurrence of cerebrovascular ischaemic strokes; on the contrary, at three months' follow up the analysis revealed a statistical significant relationship between previous anticoagulant therapy and the recurrence of ICH (p=0.055). Age, but not sex, is associated with 3-month mRs, mortality and patient institutionalization (p=0.0003, 0.024 and 0.017 respectively).

Haemorrhage characteristics: at three months' follow up, the analysis showed a trend of significant association between haemorrhage location and the occurrence of ischaemic events, with previous lobar ICH patients seeming to have a higher occurrence of ischaemic strokes than deep haemorrhage patients (p=0.063), while haematoma location did not seem to predict the recurrence

of ICH, or mRs at three months, mortality and institutionalization. Baseline haematoma volume was associated with 3-month mRs ($p<0.0001$), mortality ($p=0.0004$) and institutionalization ($p=0.0028$). The presence at admission of intraventricular expansion was associated with 3-month mRs ($p=0.0008$), mortality ($p=0.0018$), but not with institutionalization.

Admission data: the analysis showed a significant association between INR values and reversal therapy and 3 months recurrence of ICH ($p=0.034$ and 0.051 respectively). NIHSS at presentation was associated with three-month mRs ($p<0.0001$), mortality ($p<0.0001$) and institutionalization ($p=0.079$).

4.4 Haematoma expansion and outcome at three months:

Haematoma expansion was associated with 3-month mRs ($p=0.0071$) and mortality ($p=0.0018$).

At multivariate analysis, age, haemorrhage characteristics, as baseline volume and ventricular invasion, haematoma expansion and clinical severity confirmed their role as predictors of clinical outcome at 3 months: a patient aged ≥ 80 y had nearly 5 times the risk of high mRs/mortality at three months compared with younger patients (OR=4.91, 95% CI: 2.298 ; 10.489); a one point increase in baseline haematoma volume (evaluated in mL) corresponded to a 1.052-fold increase in high mRs/mortality at three months (OR=1.052, 95% CI: 1.008 ; 1.097); the presence at admission of ventricular invasion added a 2.899-fold risk of high mRs/mortality at three months (OR=2.899, 95% CI: 1.108 ; 7.586); an increase of 1 point in NIHSS score added a 1.142-fold risk of a high mRs/mortality at three months (OR=1.142, 95% CI: 1.071 ; 1.219). Patients with significant haematoma expansion had a 3-fold risk of a high mRs and mortality at three months compared with patients who did not (OR=3, 95% CI: 1.357 ; 6.633).

4.5 Predictors of outcome at one year:

For associations between variables and outcome see Table 3.

Demographic characteristics: at one year follow up, a history of diabetes mellitus was associated with the occurrence of ischaemic events, such as a history of anticoagulant therapy (p=0.098 and 0.036, respectively). Conversely, no associations emerged between demographic characteristics and one-year recurrence of ICH. Age confirmed its role in predicting outcome, in particular it was associated with one year mRs (p=0.0003), mortality (p=0.0005) and institutionalization (p=0.042). Female sex is significantly associated with institutionalization at one year (p=0.0076).

Haemorrhage characteristics: while haematoma location did not predict one-year outcome or occurrence of cerebrovascular strokes, the haematoma baseline volume was associated with mRs and mortality at one year (p<0.0001 for both), such as intraventricular invasion (p< 0.0001 both).

Admission data: administration of reversal therapy at admission was associated with a one-year occurrence of an ischaemic stroke, while INR values and reversal therapy with the recurrence of ICH at one year (p=0.028 and 0.022). Clinical severity at admission evaluated with the NIHSS score were associated with mRs and mortality at one year (p<0.0001 both).

4.6 Haematoma expansion and outcome at 1 year

Haematoma expansion was associated with mRs (p=0.035) and mortality (p=0.011) at one year.

At multivariate analysis, age, haemorrhage characteristics as baseline volume and ventricular invasion, haematoma expansion and clinical severity, confirmed their role in influencing clinical outcome at one year: a patient aged ≥ 80 y had a greater than 3-folds risk of a high mRs/mortality at one year compared with a younger patient (OR=3.277, 95%CI: 1.690 ; 6.354); one point increase in baseline haematoma volume (evaluated in mL) corresponded to a 1.046-fold increase in the risk of a high mRs/mortality at one year (OR=1.046, 95% CI: 1.009 ; 1.084); the presence of ventricular invasion at admission added a 2.760-fold risk of a high mRs/mortality at one year (OR=2.76, 95% CI: 1.122 ; 6.790); a 1-point increase in the NIHSS score added a 1.116 fold risk of a high mRs/mortality at one year (OR=1.116, 95% CI: 1.057 ; 1.178).

5. DISCUSSION

Our study is based on a population with defined characteristics: Caucasian patients, admitted to a Neurology ward (Stroke Unit) for whom surgical therapeutic options were excluded. Analysis of the results of this study must take account of these factors. In this analysis, the clinical and epidemiological characteristics of our ICH population confirm previous data in the literature and thus our participating patients could represent a reliable study population for investigating haematoma expansion variables and outcome.

As for the majority of cerebrovascular pathologies, the incidence of ICH increases with age: our population is relatively old (mean age 74.6 y), and male patients tend not only to be more affected by ICH, but to be affected at a youger age. A previous study of sex differences in incidence and pathophysiology in primary ICH[149] reported a higher male incidence and a younger mean age in men than in women at ICH onset. Our study confirms the presence of a different cerebrovascular risk factor profile between the sexes, where women are older and men are more affected by alcohol abuse, smoking and obesity[66,50]. In our population, 1/3 of ICHs occurred during antiplatelet therapy (APT) and 1/4 during anticoagulation therapy (vitamin k antagonists) and patients presenting ICHs are known to be more commonly on antiplatelet than on anticoagulant therapy[69]. Although APT is highly effective in primary or secondary prevention of coronary artery diseases and strokes, patients on antiplatelet therapy are at increased risk of intracerebral haemorrhage (ICH). This risk increases with the incremental rising in antiplatelet dose (and from single to dual or triple therapy), with NSAIDs or concomitant SSRI assumption, and with long term antiplatelet therapy use (> 1 year), with a threshold effect[69,76,26]. However, these results require verification with platelet activity assays. Antiplatelet therapy is also an independent predictor of cerebral microbleeds, which are in turn predictors of future ICHs[141]. However, apart from a possible influence on ICH incidence and pathophysiology, single antiplatelet therapy does not seem to influence intrahospital mortality and outcome (in contrast with dual antiplatelet therapy), as confirmed by our analysis (see later).

Median baseline haematoma volume was 6.3 mL, median NIHSS score was 8 (representing a mild-moderate severity score) and, as expected, NIHSS score correlated with baseline haematoma volume (see later): our population was characterized by small volume haematomas and mild-moderate clinical severity. Moreover, almost all ICHs were lobar or deep, and the characteristics did not differ between the sexes, age groups or in patients with previous antithrombotic therapy. Intraventricular invasion at baseline was present in 17.5% of our population. Considering these ICH and demographic characteristics (mean age <80 y, a mild-moderate clinical severity score, a high prevalence of lobar and deep ICHs as opposed to infratentorial, and small volume ICHs), our population could appear at baseline to be at low risk of poor outcome, according to reported prognostic scores for detecting early mortality after ICH[56,18,146,63]. In our population, 28% of ICH patients underwent significant haematoma expansion, in keeping with previous studies on spontaneous haemorrhagic strokes that revealed a percentage ranging between 22.9 and 37%[25]. This finding has previously been interpreted as "not all ICH patients have the same risk of haematoma expansion", although this hypothesis could to some extent contrast with the pathogenesis of ICH as traditionally described. Unlike subarachnoid haemorrhage, intracerebral haemorrhage does in fact develop gradually with an avalanche-type effect and signs/symptoms develop in the course of minutes, hours or even days. The concept of haematoma expansion is thus intrisic to ICH pathogenesis. So, why do ICH patients not all show haematoma expansion at control CT scan? Maximum haematoma expansion has been observed in early presentations (within 6 hours)[81,68] and in our study we selected patients with a defined onset-to-CT scan time (<12 h). But defining symptoms onset is not always so easy. In elderly patients, who usually have several comorbidities and may have pre-morbid neurological deficits (dementia, previous stroke), the exact onset can be misdiagnosed. In addition, we defined "symptoms onset" as the onset of a measurable neurological deficit, excluding non-specific symptoms (such as headache during elevated BP levels, or "more confused state" preceding the onset of sensory-motor or cortical deficits). Consequently, considering the pathophysiology of ICH, the exact timing of onset could be misdiagnosed, and what

we considered to be "onset" could instead have been the "breakthrough time," where the haematoma's avalanche type growth becomes clinically manifest. Hence, patients could have been evaluated later than thought and CT scan at admission could have shown an already established haematoma. We speculate that the exact symptoms onset could be biased in several ICH expansion studies, and that the bias could be intrinsically associated with ICH pathophysiology.

Our study showed a higher percentage of significant haematoma expansions in males and patients with high NIHSS scores at admission. In particular, male patients were twice as likely to develop haematoma expansion as female patients, and the probability of having HE increased one-fold with each one-point increase of the NIHSS score. Male patients tended to have a higher incidence of ICH, at a younger age, and a higher probability of haematoma expansion, as also shown in a recent study[83]. As regards vascular risk factors, they suffer from alcohol abuse, smoking and obesity more than female ICH patients, but none of these anamnestic data correlated directly with haematoma expansion in our analysis. The relationship between sex and HE must be mediated by some other, still unindentified factor. Female gonadal steroids have demonstrated neuroprotectve effects in preclinical works[78] which may delay the onset of ICH among women[149], protecting them from vessel rupture through their role in lipid metabolism and vasomotor responses in vessel walls [118,98,99]. A difference between the sexes in neuroinflammatory response in cerebrovascular disease has also been hypothesized[124] but, to date, these conclusions are still only speculative.

The role of clinical severity (NIHSS score) in influencing HE is also not clear although it has been reported and incorporated in the previous PREDICT A and B scores with GCS (GCS and NIHSS are often related clinically)[63]. Greater NIHSS scores reflect larger ICH volumes and a deep ICH location, and together these two factors could influence HE because of greater secondary vessel injury[18,146,63].

No significant correlations seem to exist between haematoma expansion and history of vascular risk factors, previous antithrombotic treatment, haematological parameters and blood pressure values at admission, nor is there any direct relationship with haematoma characteristics, such as location and

baseline volume. This "illogical" result is partly in line with previous studies and trials that failed to demonstrate achievement of a clear benefit from reducing the primary outcome rate (death and severe disability) through aggressive BP control, or strict glycaemic control, while the lack of a relationship between previous anticoagulant therapy and HE could be the result of an efficient reversal therapy.

In our population, three-month mortality was 25% with an additional 10% of institutionalized patients; in the first three months, 5% of ICH patients experienced a new cerebrovascular event, with an equal distribution between haemorrhagic and ischaemic strokes, and median mRs defined a dependent patient. Mortality slightly increased at one year (28.4%), as did institutionalization (19.2%); only 27% of patients were independent (mRs 0-2), median mRs was 4 for both sexes, and about 10% of ICH patients experienced a new cerebrovascular disease with a slight predominance of ICH relapses.

At baseline we defined our population at low risk of poor outcome according to prognostic scores reported in literature. Our outcomes were in fact slightly better than previous reports. Earlier studies and meta-analyses found that 1-month case fatality after ICH had remained unchanged for several decades at around 40%, and up to 54% at one year [137,1,41], where predictors of death were increasing age, decreasing GCS score, increasing ICH volumes, presence of IVH and deep/infratentorial ICH location (which are the main components of the ICH score)[108]. A systematic review of long-term outcome after ICH reported a higher annual risk of recurrent ICH (2.3%) than of ischaemic stroke (1.1%)[9] . In Poon et al's meta-analysis[108], the annual risk of recurrent ICH varied from 1.3% to 7.4%, risk seemed to be higher after lobar than after non-lobar ICH, and the risks of recurrent ICH and ischaemic stroke after ICH were not significantly different. Our outcome results, obtained by analyzing an elderly Caucasian population, confirm the reliability of previous prognostic scores in predicting outcome after an ICH, and the high ICH-related morbidity and mortality, even in a population with small haematoma volumes admitted to a Neurological ward (and not an intensive care unit). Recurrence of a new cerebrovascular event at one-year follow up affects 1 patient in 10,

with a slight prevalence of ICH relapse. In our opinion, this prevalence alone is not high enough to guide medical decision making after the first intracerebral haemorrhage, particularly with respect to the resumption of antithrombotic (antiplatelet or anticoagulant) therapy. Current Italian guidelines[65] state that ICH patients with non-valvular atrial fibrillation should resume anticoagulant therapy with a NOAC between 10 and 30 weeks from the index event (before 10 weeks in patients at high thromboembolic risk and after 30 weeks in patients at high risk of haemorrhage), with absolute contraindication post CAA-related lobar ICH . A meta-analysis by Murthy and colleagues[95] found no apparent heightened risk of ICH recurrence with administration of anticoagulant medications, but, as the authors stated, these findings may have been influenced by certain limitations in the published literature. Randomized clinical trials are warranted in this setting, partly considering the advent of NOACs. A recent Cochrane Review[103] found some evidence on the short-term effects of antithrombotic drugs after ICH but no evidence on the effects of long-term treatment. The Review concluded that "the available evidence.....neither supports nor discourages the use of short-term antithrombotic treatment after ICH. There are no published RCTs on long-term antithrombotic treatment after ICH... At the present time, clinicians will have to use other sources of information to support clinical judgements". In this respect, a recent work by Charidimou and colleagues on the burden and distribution of cerebral microbleeds in ICH (CAA-related and CAA-unrelated)[23] helped to identify patients at higher risk of ICH recurrence after an ICH, even in CAA-related patients. We believe that ICH is a mulfactorial, varied pathology, as is ischaemic stroke, but one which is less understood, and general indications or recommendations should thus be avoided. We suggest that every ICH patient should undergo complete history-taking, blood work and a clinical and radiological study before considering starting or resuming antithrombotic therapy, in order to perform highly selective risk stratification. An MRI study of small vessel disease burden and distribution, a clear definition of the causes and circumstances of ICH, and an analysis of vascular risk factors and thromboembolic risk should be included in every patient assessment.

As compared to previous studies and meta-analyses[56,108,137,116], age, in our population was confirmed to be the only demographic characteristic that strongly influenced 3-month outcome (mRs, mortality and institutionalization) although it did not influence haematoma expansion: a patient aged ≥ 80 y has nearly a 5-fold risk of high mRs/mortality at three months compared with a < 80-year-old patient. The role of baseline haematoma volume and intraventricular invasion in predicting a poor outcome (mRs and mortality) in ICH patients is in line with previous reports[56,108,137]. Specifically, in our population with small baseline haematoma volumes at presentation, the presence of ventricular invasion at admission added nearly a 3-fold risk of a high mRs/mortality at three months. The role of haematoma expansion in influencing outcome is also well recognized[17,47,25] and was confirmed in our study: patients with significant haematoma expansion had a 3-fold risk of high mRs and mortality at three months compared with patients who did not present significant haematoma expansion. Among the admission data collected, the only prognostic factor was the clinical severity score based on the NIHSS, which in turn reflected haematoma volume and location. Previous reports considered the Glasgow Coma Scale to be a marker of clinical severity[108], and showed that a low GCS score was predictive of a worse outcome. So GCS score is part of some reliable clinical prognostic scale, such as the ICH score[56]. The NIHSS score is a less studied parameter in ICH prognosis and outcome, and our study has confirmed its reliability not only as a marker of clinical severity (as currently used in clinical practice) but also as a prognostic factor in ICH patients.

On the other hand, our analysis did not, in some cases, yield the expected associations. First of all, despite demonstrating differences in risk factor profile, ICH incidence and risk of HE, the differing hormonal production and consequent neuroprotective effect assumed to exist between the sexes has not to date been clearly demonstrated to influence patient outcome after ICH, either in the literature or in our population[34,66,50]. Female sex correlated with institutionalization at one year but had no influence on mRs and mortality, and this data could be interpreted, in our opinion, as having a cultural and/or social explanation. None of the anamnestic data seem to influence outcome,

particularly a history of antithrombotic therapy (which in our study did not seem to influence haematoma volume either...). There also appears to be no correlation between haematoma location and prognosis.

Our analysis shows less clear results regarding the occurrence at follow up of an ischaemic or new haemorrhagic stroke. The occurrence of an ischaemic stroke seems to be influenced by a history of diabetes mellitus and a history of atrial fibrillation (previous anticoagulation therapy, an elevated INR and reversal therapy at admission correlate with the occurrence of an ischaemic stroke and could be considered a proxy of atrial fibrillation), and, less clearly, by a previous lobar ICH. On the other hand, an ICH relapse correlated with previous anticoagulant therapy, elevated INR values and reversal therapy at admission. The difficulties in determining the most adequate therapeutic strategy after ICH, particularly with regard to antithrombotic therapy resumption, are confirmed by these results.

The role of ICH location is not completely understood in our analysis: haematoma location did not seem to be influenced by patients' age and was not correlated with haematoma expansion and outcome, or with the recurrence of ICH, as we would have expected considering that lobar intracerebral haemorrhage is a possible indicator of CAA pathology. Moreover, infratentorial haemorrhage has been recognized as the location associated with poor outcome[56,108], but this did not emerge from our analysis. This could be attributed to the low percentage of infratentorial haemorrhages in our population, but further studies are needed to explore the role of haematoma location in ICH patients in determining prognosis and outcome. Recent studies have drawn researchers' attention to a more precise definition of haematoma location according to outcome, which goes beyond the old classification of lobar vs deep, cerebellar and brainstem haemorrhages[27,24,31]. More information is needed.

Our analysis has some limitations, specifically our population is characterized by older age and quite small haematoma volumes; this is partly due to the decision to include patients admitted to a neurology ward and not an ICU or neurosurgical department. On the other hand, this is not merely a

potential selection bias: our study reflects a well-defined scenario of the characteristics and outcome of ICH patients not eligible for a surgical approach but only for medical treatment and monitoring. Some statistical analyses could have failed to demonostrate a significant association because the sample size was, in some case, too small (e.g. a low proportion of patients with of infratentorial location). This limit could possibly be overcome on the implementation of our population in a future multicentre analysis project.

6. CONCLUSIONS and PARADOXES

In conclusion, our population of ICH patients admitted to a Neurology ward is characterised by older aged Caucasian patients with a slight prevalence of males, small haematoma volumes and mild-moderate clinical severity, with no surgical indications at baseline. At admission, this population seemed to be at low risk of poor outcome based on prognostic severity scores. The primary aim of our study was to evaluate the "haematoma expansion phenomenon" with its risk factors and its correlation with outcome. This analysis further confirmed the complexity of the phenomenon - which still remains partially unknown - and several paradoxes emerged. Moreover, we focused our attention on ICH outcome and possible prognostic factors that could guide subsequent therapeutic trials with the aim of modifying the prognosis of ICH. As regards outcome, our study confirmed that ICH patients have poor outcome, but our population had slightly better results than suggested by its baseline characteristics. The highest risk of mortality is early, in the first three months, and outcome indicators are age, clinical severity evaluated by NIHSS, baseline haematoma volume and the presence of intraventricular invasion at admission. None of these factors is modifiable at the time of medical evaluation. More studies are needed to positively influence these patients' prognosis. In addition, our study showed a higher risk of ICH relapse at follow up than of the risk of ischaemic strokes, but this data is not robust enough to guide

therapeutic choices. We strongly believe that each ICH patient should have complete bloodwork and clinical-radiological assessment in order to make the best medical choice.

We wish to conclude our analysis with some questions emerging from our study and which we hve called the "haematoma expansion paradoxes":

Male and female patients have different ages, vascular risk factors, incidence of pathology and risk of haematoma expansion, but sex does not seem to influence outcome. How can we explain this paradox?

Previous antiplatelet or anticoagulant therapy increases ICH risk but does not seem to influence haematoma expansion and outcome. How can we explain this paradox?

Haematoma expansion is a concept intrinsically connected with ICH pathophysiology and sometimes the definite onset of symptoms cannot be clearly detected. Can haematoma expansion really be considered a prognostic factor or could it represent a step in the natural history of every ICH?

ICH pathology and haematoma expansion phenomenon are not still sufficiently understood.

APPENDIX

Case 1: The meaning of "significant haematoma expansion"...

An 82-year-old woman was admitted to the Emergency Department (ER) for acute onset of left hemiparesis, which occurred half an hour after awakening. She denied headache, nausea or vomiting. A CT scan performed at ER admission (Fig 4, A), at 1.5 hours from symptoms onset, revealed a right-sided thalamic haematoma. The patient was admitted to the Stroke Unit of the Neurology ward. Her past medical history was significant for diabetes mellitus and she was taking anticoagulant therapy because of a previous pulmonary embolism due to a deep venous thrombosis. At admission she presented a Glasgow Coma Scale score of 15 and her NIHSS score was 11; serum glucose level was 220 mg/dl, INR was 2.71. Her BP was elevated (200/100 mmHg) and was corrected with administration of antihypertensive intravenous treatment (urapidil); as reversal therapy she underwent infusion with Vitamin k and three-factor Prothrombin Complex. Three hours from symptoms onset she rapidly worsened, developed a GCS score of 6, anisocoria and oxygen desaturation. A control CT scan showed a significant haematoma expansion with ventricular invasion (Fig 4, B). She was intubated and transferred to the ICU department where died some days later.

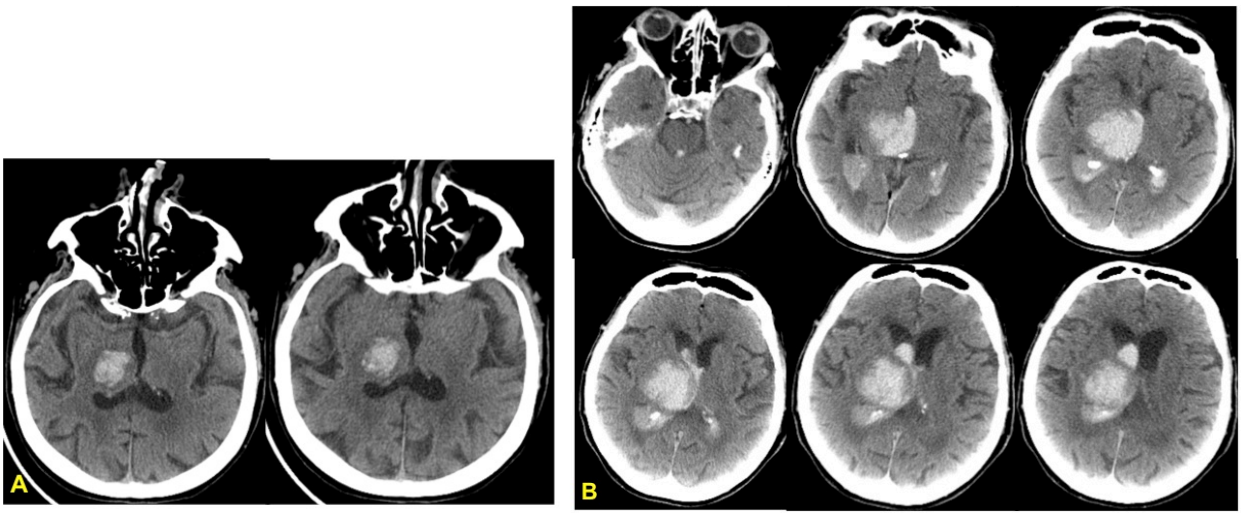

Fig 4. CT scan case 1 CT scan A at ER admission (1.5 hours from symptoms onset) showing a right thalamic haematoma. CT scan B at 3 hours from symptoms onset showing significant haematoma expansion with ventricular invasion.

Case 2: A case of chronically expanding haematoma expansion.

In 2012, a 58-year-old man was admitted to the Emergency Department for frontal headache followed, a few hours later, by acute onset of aphasia and mild right-sided hemiparesis. He suffered from hypertension and at ER admission his BP was 160/80 mmHg; he presented a Glasgow Coma Scale score of 15, serum glucose level was 104 mg/dl, INR was 1.09. A CT scan performed at ER admission showed a left temporal intracerebral haemorrhage (lobar, atypical location) associated with a thin subdural haematoma (Fig 5).The patient was admitted to the Neurology ward where he underwent CT angiography which excluded aneurysms or vascular malformations (confirmed at angiography), an MRI study which confirmed the intracerebral haematoma without other lesions. At hospital discharge, he presented mild aphasia without sensory-motor deficits. Since then, he has complained of frequent episodes of paresthesias in the right hand, with "a march progression" to the whole arm and to the right side of the mouth. Assuming focal sensory seizures he was treated with several antiepileptic drugs with partial clinical response; in addition, three years after ICH he started antiplatelet therapy.

In February 2017 he was admitted to an ER for recurrent episodes, during the previous two days, of paresthesias of the left eyebrow. A CT scan showed a convexal subarachnoideal haemorrhage (cSAH) in the right hemisphere with involvement of the right central sulcus (Fig 6 A). Antiplatelet therapy was suspended, repeated CT angiography, MRI and angiography did not find any vascular malformations. During follow up, he presented a new episode of paresthesias in the last two fingers of the left hand with dysarthria and brief alteration of consciousness. A new CT scan performed in March 2017 showed a right-sided frontal cortical-subcortical intracerebral haemorrhage at the site of the previous cSAH (see Fig 6 B). In this case, ICH occurred as an expansion of cSAH into the brain parenchyma. Lobar ICH worsened in volume and perihaematomal oedema during the days

that followed. The patient gradually developed a left-sided hemiparesis. MRI imaging (Fig 6) and clinical history were highly suggestive of CAA.

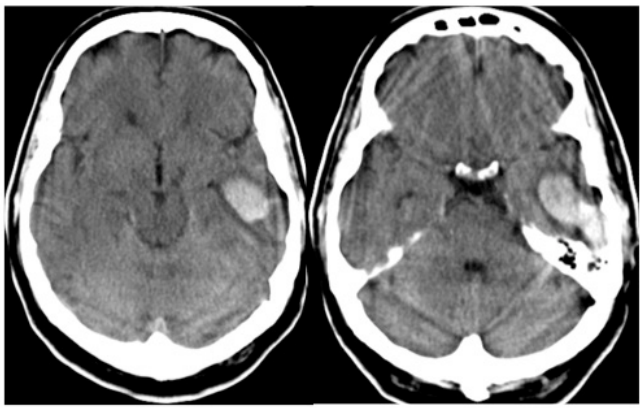

Fig 5: 2012 CT scan showing a left temporal intracerebral haemorrhage.

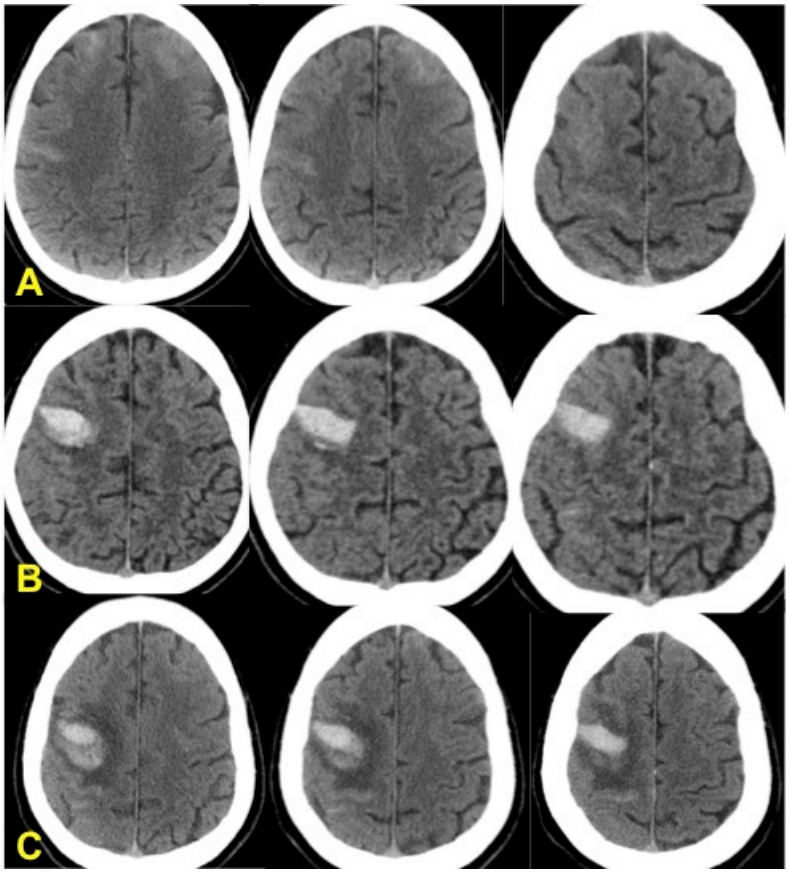

Fig 6: CT scan A performed in February 2017 showed a convexal subarachnoideal haemorrhage (cSAH) in the right hemisphere with involvement of the right central sulcus. CT scan B performed in March 2017 showed a right-sided frontal cortical-subcortical intracerebral haemorrhage at the site of previous cSAH, which developed slow haematomal expansion and perihaematomal oedema (C).

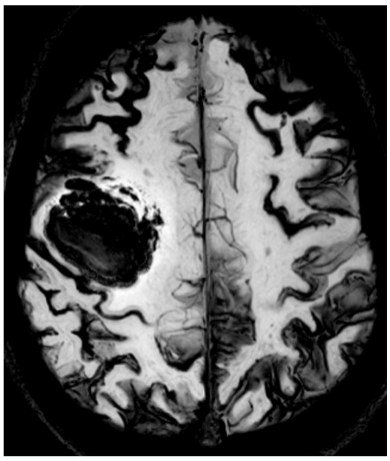

Fig 7: Brain MRI, SWI sequences showing an intracerebral pre-central frontal haemorrhage with diffuse cSAH and siderosis.

				UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS	
VARIABLE	**LEVEL**	**OVERALL, n=206**	**missing**	**SIGNIFICANTHE**	**NON SIGNIFICANTHE**	**p value**	**OR (95% CI)**	**p value**
DEMOGRAPHIC								
age (years)	median (IQR)	75 (70-82)	0	77 (71-81)	75 (69-82)	0.33		
sex M % , F %		55, 45	0	34, 23	66, 77	0.08	2.095 (1.081-4.061)	0.02
PRE-ADMISSION DATA								
history of hypertension % (n°)		80 (165)	1	27 (45)	73 (120)	0.33		
history of diabetes mellitus % (n°)		21 (43)	1	26 (11)	74 (32)	0.60		
history of hyperlipidemia % (n°)		55 (113)	2	28 (32)	72 (81)	0.89		
current smoking % (n°)		8 (14)	34	29 (4)	71 (10)	1		
obesity % (n°)		27 (31)	92	26 (8)	74 (23)	0.85		
alcohol abuse % (n°)		16 (29)	21	28 (8)	72 (21)	0.88		
antiplatelet therapy % (n°)		33 (68)	1	29 (20)	71 (48)	0.88		
anticoagulant therapy % (n°)		24 (50)	0	20 (10)	80 (40)	0.12		
HAEMORRHAGE								
haemorrhage location			0			0.73		
deep % (n°)		51.9 (107)		30 (32)	70 (75)			
lobar % (n°)		41.3 (85)		29 (25)	71 (60)			
cerebellar % (n°)		4.9 (10)		20 (2)	80 (8)			
brainstem % (n°)		1.9 (4)		0 (0)	100 (4)			
ventricular invasion % (n°)		17.5 (36)	0	33 (12)	67 (24)	0.49		
haematoma volume mL	median (IQR)	6.3 (2.5-13.5)	0	6.9 (2.9-12.5)	6 (2.2-14.4)	0.72		
ADMISSION DATA								
SBP mmHg	mean (SD)	168 (31)	8	166 (31)	169 (30.9)	0.62		
DBP mmHg	mean (SD)	89 (18)	4	90 (80-100)	90 (75-100)	0.87		
blood glucose mg/dL	median (IQR)	117 (104-142)	1	118 (104-145)	117 (103-142)	0.83		
total cholesterol mg/dL	mean (SD)	190 (44)	3	191 (44)	189 (43.6)	0.78		
HDL cholesterol mg/dL	median (IQR)	52 (42-65)	14	51 (39-67)	53 (45-64)	0.45		
LDL cholesterol mg/dL	median (IQR)	114 (87-137)	21	119 (91-137)	113 (84-138)	0.55		
INR	median (IQR)	1 (1.1-1-29)	0	1.04 (1-1.1)	1.1 (1-2.03)	0.059		
platelet count	median (IQR)	211 500 (178 000-256 000)	0	205 000 (176-257 000)	213 000 (178-256 000)	0.80		
NIHSS	median (IQR)		4	14 (6-19)	8 (3-14)	0.001	1.082 (1.037-1.130)	0.0003
MANAGEMENT								
reversal therapy		23.7 (49)	0	20 (10)	80 (39)	0.14		

Table 1: Characteristics of the study population and differences between patients with and without significant haematoma expansion

VARIABLE	3-MONTH FOLLOW UP					MULTIVARIATE ANALYSIS		
DEMOGRAPHIC	**ischaemic events**	**new ICH**	**mRs (0-2/3-4/5-6)**	**mortality**	**instituzionalization**	**OR**	**CI 95%**	**p value**
age (years)	p=0.57	p=0.46	p=0.0003	p=0.024	p=0.017			
age (years) (<60/60-79/>=80)	p=0.72	p=0.72	p=0.012	p=0.048	p =0.20			
age (years) (<80/>=80)	p=0.62	p=0.62	p=0.014	p=0.044	p=0.12	4.91	2.298-10.489	<0.0001
sex M % , F %	p=1.0	p=0.63	p=0.32	p=0.71	p=0.67			
PRE-ADMISSION DATA								
history of hypertension % (n°)	p=0.55	p=1.0	p=0.39	p=0.89	p=0.46			
history of diabetes mellitus % (n°)	p=0.55	p=1.0	p=0.23	p=0.81	p=1.0			
history of hyperlipidemia % (n°)	p=1.0	p=1.0	p=0.54	p=0.27	p=0.057			
current smoking % (n°)	p=1.0	p=1.0	p=0.14	p=1.00	p=1.0			
obesity % (n°)	p=1.0	p=0.50	p=0.28	p=0.77	p=0.49			
alcohol abuse % (n°)	p=1.0	p=0.47	p =0.084	p=0.40	p=0.20			
antiplatelet therapy % (n°)	p=0.63	p=1.0	p=0.62	p=0.99	p=0.95			
anticoagulant therapy % (n°)	p=0.28	p=0.055	p=0.36	p=0.18	p=0.34			
HAEMORRHAGE CHARACTERISTICS								
haemorrhage location	p=0.063	p=0.49	p=0.97	p=0.90	p=0.88			
deep % (n°)								
lobar % (n°)								
cerebellar % (n°)								
brainstem % (n°)								
ventricular invasion % (n°)	p=1.0	p=1.0	p=0.0008	p=0.0018	p=0.23	2.899	1.108-7.586	0.0301
haematoma volume mL	p=0.75	p=0.59	p <0.0001	p=0.0004	p=0.0028	1.052	1.008-1.097	0.0200
haematoma volume mL (<=10/11-20/21-30/>30)	p=0.33	p=0.33	p=0.0069	p=0.023	p=0.013			
ADMISSION DATA								
SBP mmHg	p=0.62	p=0.93	p=0.17	p=0.099	p=0.85			
DBP mmHg	p=0.53	p=0.46	p=0.16	p=0.15	p=0.41			
blood glucose mg/dL	p=0.40	p=0.99	p=0.36	p=0.92	p=0.55			
total cholesterol mg/dL	p=0.65	p=0.67	p=0.50	p=0.48	p=0.51			
HDL cholesterol mg/dL	p=0.75	p=0.96	p=0.79	p=0.50	p=0.27			
LDL cholesterol mg/dL	p=0.57	p=0.88	p=0.98	p=0.86	p=0.58			
INR	p=0.60	p=0.034	p=0.36	p=0.33	p=0.62			
platelet count	p=0.76	p=0.51	p=0.14	p=0.091	p=0.42			
NIHSS	p=0.25	p=0.18	p<0.0001	p <0.0001	p=0.079	1.142	1.071-1.219	<0.0001
MANAGEMENT								
reversal therapy	p=0.27	p=0.051	p=0.36	p=0.18	p=0.11			
HAEMATOMA EXPANSION	p=0.32	p=1.0	p=0.0071	p=0.0018	p=0.75	3	1.357-6.633	0.0067

Table 2: Associations between variables and three-month outcome.

VARIABLE	ONE YEAR FOLLOW UP					MULTIVARIATE ANALYSIS		
DEMOGRAPHIC	**ischaemic events**	**new ICH**	**mRs (0-2/3-4/5-6)**	**mortality**	**instituzionalization**	**OR**	**CI 95%**	**p value**
age (years)	p=0.96	p=0.39	p=0.0003	p=0.0005	p=0.042			
age (years) (<60/60-79/>=80)	p=1.00	p=0.84	p=0.0007	p=0.0034	p=0.29			
age (years) (<80/>=80)	p=1.0	p=0.70	p=0.0071	p=0.0023	p=0.52	3.277	1.690-6.354	0.0004
sex M % , F %	p=0.42	p=0.72	p=0.11	p=0.81	p=0.0076			
PRE-ADMISSION DATA								
history of hypertension % (n°)	p=1.00	p=0.21	p=0.78	p=0.68	p=0.0055			
history of diabetes mellitus % (n°)	p=0.098	p=1.00	p=0.73	p=0.42	p=1.00			
history of hyperlipidemia % (n°)	p=1.00	p=1.00	p=0.68	p=0.68	p=0.73			
current smoking % (n°)	p=1.00	p=1.00	p=0.37	p=0.29	p=0.68			
obesity % (n°)	p=0.12	p=0.53	p=0.81	p=0.67	p=0.49			
alcohol abuse % (n°)	p=0.59	p=1.00	p=0.31	p=0.18	p=1.00			
antiplatelet therapy % (n°)	p=1.00	p=0.25	p=0.26	p=0.23	p=0.30			
anticoagulant therapy % (n°)	p=0.036	p=0.11	p=0.44	p=0.21	p=0.038			
HAEMORRHAGE CHARACTERISTICS								
haemorrhage location	p=0.26	p=0.36	p=0.46	p=0.38	p=0.16			
deep % (n°)								
lobar % (n°)								
cerebellar % (n°)								
brainstem % (n°)								
ventricular invasion % (n°)	p=1.0	p=0.60	p< 0.0001	p<0.0001	p=0.71	2.76	1.122-6.790	0.0271
haematoma volume mL	p=0.50	p=0.63	p<0.0001	p<0.0001	p=0.19	1.046	1.009-1.084	0.015
haematoma volume mL (<=10/11-20/21-30/>30)	p=0.25	p=0.40	p=0.0019	p=0.0095	p=0.30			
ADMISSION DATA								
SBP mmHg	p=0.36	p=0.46	p=0.19	p=0.22	p=0.94			
DBP mmHg	p=0.34	p=0.43	p=0.058	p=0.024	p=0.036			
blood glucose mg/dL	p=0.81	p=0.41	p=0.19	p=0.12	p=0.66			
total cholesterol mg/dL	p=0.74	p=0.68	p=0.21	p=0.079	p=0.30			
HDL cholesterol mg/dL	p=0.52	p=0.99	p=0.26	p=0.17	p=0.17			
LDL cholesterol mg/dL	p=0.77	p=0.98	p=0.51	p=0.27	p=0.27			
INR	p=0.12	p=0.028	p=0.16	p=0.058	p=0.32			
platelet count	p=0.88	p=0.15	p=0.018	p=0.0074	p=0.025			
NIHSS	p=0.28	p=0.64	p<0.0001	p<0.0001	p=0.013	1.116	1.057-1.178	<0.0001
MANAGEMENT								
reversal therapy	p=0.032	p=0.022	p=0.39	p=0.17	p=0.046			
HAEMATOMA EXPANSION	p=0.34	p=0.41	p=0.035	p=0.011	p=0.62			

Table 3: Associations between variables and one-year outcome.

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