Challenges and controversies in the medical management of primary and antithrombotic-related intracerebral hemorrhage

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Abstract: Intracerebral hemorrhage (ICH) represents 10–15% of all cerebrovascular events, and is associated with substantial morbidity and mortality. In contrast to ischemic cerebrovascular disease in which acute therapies have proven beneficial, ICH remains a more elusive condition to treat, and no surgical procedure has proven to be beneficial. Aspects pertinent to medical ICH management include cessation or minimization of hematoma enlargement, prevention of intraventricular extension, and treatment of edema and mass effect. Therapies focusing on these aspects include prothrombotic (hemostatic) agents, antihypertensive strategies, and antiedema therapies. Therapies directed towards the reversal of antithrombosis caused by antiplatelet and anticoagulant agents are frequently based on limited data, allowing for diverse opinions and practice styles. Several newer anticoagulants that act by direct thrombin or factor Xa inhibition have no natural antidote, and are being increasingly used for various prophylactic and therapeutic indications. As such, these new anticoagulants will inevitably pose major challenges in the treatment of patients with ICH. Ongoing issues in the management of patients with ICH include the need for effective treatments that not only limit hematoma expansion but also result in improved clinical outcomes, the identification of patients at greatest risk for continued hemorrhage who may most benefit from treatment, and the initiation of therapies during the hyperacute period of most active hemorrhage. Defining hematoma volume increases at various anatomical locations that translate into clinically meaningful outcomes will also aid in directing future trials for this disease. The focus of this review is to underline and discuss the various controversies and challenges involved in the medical management of patients with primary and antithrombotic-related ICH.

Keywords: antithrombotic, challenges, controversies, hematoma expansion, intracerebral hemorrhage, medical management, primary, review

Introduction

Intracerebral hemorrhage (ICH) represents 10–15% of all cerebrovascular events [Sudlow and Warlow, 1997] and is associated with a 30-day mortality rate of approximately 40%, with an additional 40% of patients remaining disabled at 6 months [Counsell *et al.* 1995]. Various medical strategies have been proposed and studied in the treatment of primary ICH from hypertensive or amyloid arteriopathies, including prothrombotic agents to create hemostasis in ruptured vessels, antihypertensive/normotensive treatments to limit perfusion pressures into damaged vessels,

and antiedema medications to decrease perihematomal edema and mass effect.

The management of antithrombotic-associated ICH may allow for more goal-directed interventions (correction of abnormal laboratory values), but is frequently based on limited and inadequate evidence. The recent introduction of a newer generation of anticoagulants with novel mechanisms of action will inevitably provide even greater challenges to the management of patients with ICH. This article reviews the contemporary literature about the medical treatment of primary

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and antithrombotic-associated ICH, and explores current existing controversies and anticipated future challenges in the treatment of ICH.

Primary intracerebral hemorrhage

In patients with primary ICH, clinical and radiological determinants of outcome include patient age, clinical status upon presentation, ICH location and size, and intraventricular hemorrhage (IVH) [Hemphill *et al.* 2001]. Among these variables, only ICH size and IVH are amenable to intervention, given that intracerebral expansion and intraventricular extension may occur as a result of the dynamic nature of the hematoma [Steiner *et al.* 2006a; Brott *et al.* 1997]. Being that IVH represents a consequence of hemorrhage enlargement and hematoma size [Moussouttas *et al.* 2011; Hallevi *et al.* 2008], the single most addressable target in ICH management becomes the limitation of hematoma expansion during the acute phase when continued active hemorrhage is most likely to occur [Davis *et al.* 2006; Brott *et al.* 1997]. Additional possible complications of any ICH include satellite hemorrhages, hydrocephalus, edema and mass effect (Figure 1).

Predictors of hematoma expansion

In an effort to identify patients at greatest risk for hematoma expansion, and therefore those that may most benefit from acute therapeutic interventions, various clinical, laboratory and radiological factors have been investigated and identified. Determinants of hematoma expansion have included anticoagulant (warfarin) use [Flibotte *et al.* 2004], larger initial size [Broderick *et al.* 2007b], irregular shape and density [Barras *et al.* 2009], and serological evidence of systemic inflammation [Silva *et al.* 2005]. Contrast extravasation into the hematoma body, indicative of persisting vascular mural permeability and ongoing hemorrhage, has been identified as an independent predictor of hematoma enlargement and adverse outcomes [Almandoz *et al.* 2010; Goldstein *et al.* 2007; Wada *et al.* 2007].

Prothrombotic strategies

Prothrombotic strategies have centered around the use of recombinant activated factor VII (rF-VIIa), a compound originally used in the treatment of hemophilia [Roberts *et al.* 2004]. Upon injury to the endothelium, local release of thromboplastin and initial aggregation of platelets induce the conversion of VII to active VIIa,

Figure 1. Hypertensive lenticular hemorrhage in a patient taking aspirin, imaged just under 4 h from onset and reimaged 24 h after onset. Computerized tomography scans show marked enlargement of hematoma, with satellite hemorrhages, surrounding edema, substantial mass effect, intraventricular extension, and hydrocephalus caused by trapping of the left lateral ventricle.

which converts factor X to Xa, thereby initiating the extrinsic coagulation cascade that results in thrombin generation and fibrin deposition [Roberts *et al.* 2004]. In an attempt to augment local thrombosis at the site of vessel rupture, and thereby decrease hemorrhage and hematoma expansion, rF-VIIa was studied in two major trials of primary ICH.

The initial phase II study was a randomized trial of rF-VIIa (40, 80 and 160 µg) *versus* placebo in patients diagnosed using computerized tomography (CT) within 3 h of onset [Mayer *et al.* 2005]. For the nearly 400 enrolled patients, mean treatment time was 167 min. The 80 µg and 160 µg doses resulted in decreased hematoma expansion (rF-VIIa 14% and 11% *versus* placebo 29%), and decreased rates of IVH and edema at 24 h. Decreases in 90-day mortality (18% *versus* 29%), and improved functional outcomes as measured by several grading scales were also observed in the active treatment arms. However, more systemic thrombotic events occurred with rF-VIIa (7% *versus* 2%), mostly in patients receiving the 160 µg dose.

The similar phase III FAST study tested rF-VIIa (20 and 80 µg) *versus* placebo, enrolled over 800 patients, and administered treatment within a mean time of 160 min [Mayer *et al.* 2008]. Again a decrease in hematoma expansion was noted for the 80 µg group (11% *versus* 26%), yet this time no difference was noted in IVH rate, edema volume, mortality or disability (26% and 29% *versus* 24%). Possible reasons for the contrasting negative findings have included unexpected low mortality and disability in the placebo group (19% and 24%, respectively), more frequent IVH in patients receiving rF-VIIa (38% *versus* 29%), and more thrombotic (mostly coronary) complications in those receiving rF-VIIa (8% *versus* 4%).

A *post-hoc* analysis of the FAST trial identified a subgroup of patients in whom rF-VIIa 80 µg/kg may be beneficial [Mayer *et al.* 2009]. Patients younger than 70 years, with an ICH volume less than 60 ml, an IVH volume less than 5 ml, and time to treatment up to 2.5 h were found to have a lower chance of a poor outcome (Rankin score 5–6) compared with placebo (odds ratio 0.28; 95% confidence interval 0.08–1.06). A greater mean reduction in hematoma volume was also noted in comparison to the entire study group (7.3 ml *versus* 3.8 ml; $p = 0.02$).

These findings, however, are yet to be verified in a prospective trial.

Antihypertensive strategy

Antihypertensive strategies have evolved on the premise that perfusion pressure inside the vessel lumen may promote continued hemorrhage from regions with compromised mural integrity and local loss of autoregulation [Morgensetern *et al.* 2010]. However, the exact role of hypertension following acute ICH has never been definitively elucidated [Jauch *et al.* 2006] and controversy exists as to whether elevated pressures contribute to hematoma expansion, result from the hematoma causing compression of central structures and intracranial pressure elevations, or simply represent a marker of severity and worse prognosis [Morgensetern *et al.* 2010]. To date there have been two randomized trials assessing whether various ranges of systemic pressures reduce hematoma expansion and provide benefit in patients with acute ICH.

The INTERACT study enrolled over 400 patients presenting with systolic pressures of 150–180 mmHg, who were randomized within 6 h of onset to conservative (systolic <140 mmHg) *versus* liberal (systolic <180 mmHg) control [Anderson *et al.* 2008]. Goal pressures were to be achieved within 1 h of starting intravenous nicardipine, and were maintained for 24 h. Mean initial systolic pressures were similar in the two groups, and overall mean time to treatment was 4.5 h from onset. At 24 h, less ICH expansion was seen in the conservative arm (14% *versus* 36%), as well as less substantial enlargement defined as volume increase greater than 33% (15% *versus* 33%), but no difference was observed in edema volume on day 3 or on the clinical outcome mortality/disability (48% *versus* 49%) at 90 days [Anderson *et al.* 2010]. The anticipated INTERACT II study will be an open-label but assessor-blinded trial that will randomize 2800 patients presenting with systolic pressures of 150–220 mmHg to two treatment arms (systolic <140 *versus* <180 mmHg) within 6 h of ICH onset for a period of 7 days. The primary outcome will be 90-day mortality/dependency, while secondary outcomes will assess treatment within 4 h, levels of disability and quality of life.

The ATACH study randomized 80 patients with systolic pressures greater than 170 mmHg to one of three target systolic pressures (110–140, 140–

170, 170–200 mmHg) within 6 h of onset using intravenous nicardipine for 24 h [ATACH Investigators, 2010]. Preliminary results demonstrated greater rates of treatment failure, adverse events, neurologic worsening, and mortality in the most aggressively treated group. Three-month outcomes comparing dichotomized groups above and below the medians for two treatment parameters (systolic reduction at 6 h and systolic reduction area under the curve) revealed trends towards improved radiographical and clinical outcomes, but no definite advantage to aggressive treatment [Qureshi *et al.* 2010].

Various theories have been proposed to explain the failure of antihypertensive therapy to improve clinical outcomes despite mitigating hematoma expansion. Low baseline clinical severity, small initial hematoma volumes, relatively minor decreases in hematoma enlargement from active treatment, lack of impact on perihematomal edema, possible neurological deterioration from induced ischemia in vulnerable regions, inadequate study power, and hypertension as a consequence and not cause of ICH expansion have all been postulated [Anderson *et al.* 2010, 2008; ATACH Investigators, 2010; Qureshi *et al.* 2010].

Perihematomal edema and inflammation

Studies on the treatment of perihematomal edema and inflammation have used hyperosmolar and steroidal agents in an attempt to minimize or reduce regional mass effect and tissue injury. The variety of agents used speaks to the uncertainty that exists regarding the exact nature of the edema – extruded serum from hematoma coagulation and contraction, vasogenic edema from local disruption of capillary membranes, or cytotoxic cellular injury [Hoff and Xi, 2003]. Controversy also exists as to whether the diffusion restricted areas of edema on magnetic resonance imaging (MRI) represent cytotoxic edema secondary to compromised microvascular perfusion (in which case, antihypertensive therapy may be detrimental) or cytotoxic edema due to structural and biochemical damage from the hemorrhage.

Perfusion studies that demonstrated hypoperfusion to the perihematomal area were interpreted as representing penumbra with potential for ischemia [Siddique *et al.* 2002]. However, histological investigations revealed mitochondrial dysfunction without ischemia [Kim *et al.* 2006],

implying that the reduced perfusion and metabolism may indicate tissue hibernation [Qureshi *et al.* 2009]. MRI studies have characterized the perihematomal edema as predominantly extracellular [Carhuapoma *et al.* 2000], with lesser areas of cytotoxic edema unrelated to the degree of hypoperfusion and thus unlikely ischemic [Olivot *et al.* 2010]. Whether edema volume actually impacts clinical outcome remains to be determined [Arima *et al.* 2009; Gebel *et al.* 2002], thus possibly negating the need for future trials of antiedema agents in patients without substantial mass effect or intracranial hypertension.

Only two studies have tested the utility of dexamethasone in patients with ICH. The first was limited by very small patient numbers, partial open-label treatment allocation, unavailability of modern imaging techniques, inclusion of patients with hemorrhagic infarction, and the use of non-standardized clinical grading scales [Tellez and Bauer, 1973]. The second enrolled larger numbers, randomized patients in a blinded fashion, included only patients with supratentorial ICH diagnosed by CT, and stratified patients according to Glasgow Coma Scale score [Poungvarin *et al.* 1987]. No differences in mortality were noted, while greater rates of infection and hyperglycemia occurred with dexamethasone. The study was terminated prematurely.

In the first study of hyperosmolar therapy, 216 patients with primary supratentorial ICH were randomized within 24 h of onset to intravenous glycerol *versus* saline for 6 consecutive days. No difference in 180-day outcome was seen, yet anemia due to hemolysis occurred with glycerol [Yu *et al.* 1992]. Mannitol (20% 100 ml) was tested in a randomized, controlled trial of 128 patients presenting within 6 days of a primary supratentorial CT confirmed ICH [Misra *et al.* 2005]. Thirty-day mortality and 90-day functionality did not differ between the two groups. Physiological studies have failed to demonstrate an advantage to treatment with mannitol in terms of augmenting regional perfusion following ICH [Kalita *et al.* 2004].

Data from animal models and human subjects suggest that hypothermia 35°C may reduce perihematomal edema, and thus possibly concurrent neurotoxicity, via enhancement of endothelial integrity, anti-inflammatory actions and neuroprotective properties [Kollmar *et al.* 2010; MacLellan *et al.* 2006]. Potential adverse

developments, however, may include rebound edema and intracranial pressure increase [Schwab *et al.* 2001], and various multisystem complications [Polderman and Herold, 2009]. Whereas hypothermia may also theoretically attenuate any evolving perihematoma ischemia [Kollmar *et al.* 2002], the hypertension that typically accompanies hypothermia may risk ICH enlargement [MacLellan *et al.* 2004]. No randomized controlled trials have been performed.

Summary and future strategies

In conclusion, contemporary studies have demonstrated the ability of prothrombotic and anti-hypertensive modalities to reduce ICH enlargement, but not to alter clinical outcome [Qureshi *et al.* 2010; Anderson *et al.* 2008; Mayer *et al.* 2008, 2005]. This paradox may be explained by the magnitude of hematoma volume difference achieved between the treatment and placebo arms. In all studies performed, absolute volume differences between treatment groups were typically on the order of 2–5 ml, which when compared with mean hematoma volumes of 20–30 ml represents a very small fraction of the entire hemorrhagic mass.

Recent articles have attempted to define an absolute or relative volume increase which may reliably determine clinical worsening among patients with ICH, and which may be suitable for study as an endpoint in randomized trials [Dowlathshahi *et al.* 2011]. Absolute volume increases of 12 ml or more, and not relative increases, were found to have the best predictive value for clinical deterioration [Dowlathshahi *et al.* 2011]. The authors correctly concluded that many patients with ICH may not benefit from acute therapies because of the rarity of cases in which hematoma expansion exceeds 12 ml. They propose that future studies may require very large numbers of patients to demonstrate any treatment effect, or may need to selectively include only those patients at greatest risk for substantial expansion [Dowlathshahi *et al.* 2011].

Omitted from this informative review was the role that hemorrhage location and intraventricular extension play in determining clinical worsening. Posterior fossa lesions of even 3 cm diameter may cause substantial functional compromise and clinical deterioration by local compression of adjacent structures or by obstructive hydrocephalus [Morgensetern *et al.* 2010]. In addition, hemorrhages in deep paraventricular areas

(thalamus and caudate head) are typically smaller and undergo less expansion than those of the lenticular nuclei or lobar locations, yet result in similar outcomes [Moussouttas *et al.* 2011]. As such, ICH location must be considered a crucial factor in defining the ‘critical’ amount of hematoma volume that determines clinical worsening. To date, no clinical studies have addressed this issue.

Therefore, whereas cerebral ischemia represents an acute process for which successful treatment may be instituted during the first few hours following onset, ICH may represent a ‘hyperacute’ process that may necessitate treatment within the first 1 or 2 h of onset. The small increases in hematoma volumes observed in major clinical trials of patients diagnosed within 3–6 h [Qureshi *et al.* 2010; Anderson *et al.* 2008; Mayer *et al.* 2008, 2005] and the frequent evidence of IVH upon initial scanning [Steiner *et al.* 2006a] support the concept of greatest hematoma expansion within a very narrow and early time frame.

Antithrombotic-related intracerebral hemorrhage

Risk factors for antithrombotic ICH have mostly been studied in the context of warfarin use, and include age, hypertension, leukoaraiosis, amyloid angiopathy, and intensity of anticoagulation [Broderick *et al.* 2007a]. Evidence-based guidelines regarding the use of reversing agents and hematological transfusions for the management of ICH due to antithrombotic drugs are limited by incomplete and inadequate data, which has allowed for various therapeutic options and for diverse treatment preferences.

Hematoma characteristics

In contrast to primary ICH, antithrombotic hemorrhages (and, in particular, warfarin-related ICHs) demonstrate larger initial volumes and greater hematoma enlargement, likely due to more pronounced and prolonged extravasation [Cucchiara *et al.* 2008]. Antithrombotic ICHs are also more irregular in contour such that visual estimation of volume may be most accurately approximated by the equation $ABC/3$ (instead of $ABC/2$, which is typically used for nonantithrombotic hematomas) [Huttner *et al.* 2006b], where ABC represents the product of each of the longest three-dimensional diameters [Kothari *et al.* 1996]. Finally, hemorrhages related to antithrombotics frequently exhibit distinct fluid levels [Gebel *et al.* 1998], indicating

separation of plasma and cellular components because of impaired thrombus formation [Ichikawa and Yanagihara, 1998], and may be multicompartmental [Gebel *et al.* 1998]. Theoretically, less edema may develop as a result of impairment in the thrombin generation, which typically increases vascular permeability [Sansing *et al.* 2003], but this has not consistently been observed [Steiner *et al.* 2006b].

Antiplatelet agents

Controversy exists over whether ICH in the setting of antiplatelet use warrants platelet transfusion because the literature is conflicting as to whether antiplatelet agents even contribute to hematoma expansion or to adverse outcomes. Evidence that antiplatelet agents increase hematoma expansion and worsen outcome [Yildiz *et al.* 2011; Creutzfeldt *et al.* 2009; Toyoda *et al.* 2009, 2005; Lacut *et al.* 2007; Sorimachi *et al.* 2007; Saloheimo *et al.* 2006; Roquer *et al.* 2005] is countered by studies that report no increase in hematoma volume or worsened outcome [Moussouttas *et al.* 2010; Sansing *et al.* 2009; Ishibashi *et al.* 2008; Broderick *et al.* 2007b; Foerch *et al.* 2006], and by animal studies showing no differences in volumes or outcomes [Lauer *et al.* 2011].

These contrasting data may be attributed to differences in study methodology (for example, inclusion or exclusion of posterior fossa hemorrhages which may be predisposed to intraventricular extension yet undergo limited enlargement from anatomic restrictions, visual versus computerized hematoma volume measurement techniques, and outcome measures of >33% *versus* any measurable volume increase). However, the discrepancies may also be due to unreliability of reported antiplatelet use, the variety of agents used at different doses, and interindividual differences in antiaggregant activity and resistance [Naidech *et al.* 2009a]. To date, retrospective studies have failed to show benefit from platelet transfusion in patients with ICH on antiplatelet agents [Ducret *et al.* 2010; Creutzfeldt *et al.* 2009].

Presently, only small observational studies have assessed the impact of platelet inhibition, as measured by aggregometry assays, upon ICH enlargement and clinical outcome. One study identified greater hematoma expansion in patients with impaired platelet activity, as well as worse outcomes at 90 days compared with

those with normal platelet action [Naidech *et al.* 2009c]. A second study associated reduced platelet activity with the occurrence of IVH, greater ICH score, and greater risk for mortality [Naidech *et al.* 2009b]. The investigators of these studies also identified greater platelet inhibition among patients taking combination antiplatelet regimens compared with those on single agents only [Naidech *et al.* 2009a].

Unfortunately, unlike measures of anticoagulant activity [for example, international normalized ratio (INR) for warfarin or partial thromboplastin time (PTT) for heparin], no consistently reliable or globally validated method exists for quantifying the antiaggregant activity induced by antiplatelet agents [Breet *et al.* 2010], and therefore no means exists by which to select those patients who may be most at risk for continued hemorrhage, or those who may most benefit from transfusion therapy. Currently, the use of platelet transfusions in patients with ICH is unproven and is considered investigational [Morgensetern *et al.* 2010]. Potential complications of transfusion that must be considered include volume overload, transfusion reactions, anaphylaxis, acute lung injury, and infection [Refaai *et al.* 2011].

Heparin and warfarin

In reversing heparin anticoagulation, protamine remains the single most effective and only needed treatment, which can rapidly and completely normalize PTT following administration [Hirsh and Raschke, 2004]. Conversely, several treatment options exist for the management of warfarin-related ICH with elevated INR, including cobalamin, fresh frozen plasma (FFP), prothrombin complex concentrates (PCCs) and rF-VIIa. In the absence of randomized, controlled studies, diverse and varied opinions exist regarding the most appropriate therapy or combination of therapies [Steiner *et al.* 2006b]. In contrast to antiplatelet agents, warfarin use has been convincingly connected to hematoma expansion and adverse outcome [Cucchiara *et al.* 2008; Flibotte *et al.* 2004].

Cobalamin counteracts warfarin inhibition of synthetic enzymes, and provides hemostatic protection beyond the limited lifespan of administered factors [Steiner *et al.* 2006b]. Intravenous cobalamin reverses coagulopathy faster than oral dosing [Watson *et al.* 2001], and subcutaneous administration is discouraged due to

unpredictable absorption [Raj *et al.* 1999]. A dose of 10 mg is generally recommended [Morgensetern *et al.* 2010], and risk of anaphylaxis from intravenous administration is considered to be low [Fiore *et al.* 2001]. Since reversal takes several hours [Watson *et al.* 2001], concurrent administration of coagulation factors is essential. In one study, normalization of INR by 2 h occurred in 84% of patients given PCC, in 39% of those given FFP and in 0% of those given cobalamin [Huttner *et al.* 2006a]. Hematoma expansion occurred in 19%, 33% and 50% respectively.

Among coagulation factor replenishing agents, PCCs and rF-VIIa are capable of normalizing INR within minutes, whereas FFP may require hours [Morgensetern *et al.* 2010; Steiner *et al.* 2006b]. This may be because of the variable concentrations of coagulation factors provided by FFP, and therefore to variable completeness of factor repletion [Broderick *et al.* 2007a]. Treatment delays may also be encountered in the time needed for preparation and infusion of FFP [Bershad and Suarez, 2010]. Failure to achieve hemostasis following INR correction with FFP has also been observed [Lee *et al.* 2006], possibly due to persistently low factor IX levels [Makris *et al.* 1997]. FFP may also be associated with diminishing gains, whereby large amounts of FFP result in negligible INR changes when the INR is ≤ 1.5 [Holland and Brooks, 2006]. Because FFP administration can be complicated by volume overload and heart failure, transfusion reactions and anaphylaxis, and the potential for infectious transmission, some authorities have suggested alternative agents [Steiner *et al.* 2006b].

As a recombinant preparation composed of one coagulation protein, rF-VIIa lacks many of the factors inhibited by warfarin, and thus may not completely reverse warfarin anticoagulation. Studies on human subjects have demonstrated an inability for rF-VIIa to reverse warfarin-induced hemorrhagic diathesis despite normal INR [Skolnick *et al.* 2010], and experimental studies have confirmed the ability of rF-VIIa to correct the INR yet fail to restore thrombin generation [Tanaka *et al.* 2008]. The transient duration of activity and possible need for repeated dosing, in conjunction with the known systemic thrombotic complications, may also pose a substantive risk when using rF-VIIa [Broderick *et al.* 2007a]. As a result of these limitations,

neurovascular societal guidelines have discouraged the use of this drug [Morgensetern *et al.* 2010].

PCCs are an admixture of various coagulation factors, the exact composition and concentration of which varies depending on the specific formulation. However, all contain those factors inhibited by warfarin (II, VII, IX and X), and some provide a more 'physiologically balanced' preparation that includes inhibited anticoagulants (proteins C and S) [Bershad and Suarez, 2010]. Like rF-VIIa, PCCs may provide for rapid correction of INR [Dickneite, 2007] yet may also provide more complete reversal of coagulopathy [Dickneite, 2007] and less risk for thromboembolic and ischemic complications [Morgensetern *et al.* 2010; Leissinger *et al.* 2008]. PCC use may also avoid many of the complications associated with FFP [Bershad and Suarez, 2010]. As a result, leading neurovascular organizations have increasingly recommended PCCs for reversal of warfarin anticoagulation [Morgensetern *et al.* 2010].

Newer anticoagulants

The newer generation anticoagulants which act by direct thrombin inhibition or by direct Xa inhibition are administered by intravenous or oral route, and are variably indicated in the treatment of thrombotic conditions (venous thromboembolization and heparin-induced thrombocytopenia) and in preventing atrial fibrillation embolization [Levy *et al.* 2010]. These agents will be increasingly seen in the setting of ICH because of the increasing use of oral medications which, unlike warfarin, do not require routine serological monitoring, and as a result of an aging population are more predisposed towards atrial fibrillation and cerebral amyloid angiopathy [Vernooij *et al.* 2008; Go *et al.* 2001]. The major challenge with these new agents will be reversal of anticoagulation in the setting of ICH, since no natural antidote or reversing medication exists for these compounds [Levy *et al.* 2010].

Among the direct thrombin inhibitors are argatroban and the hirudin family of anticoagulants which are indicated in the setting of heparin-induced thrombocytopenia [Levy *et al.* 2010], and dabigatran which recently demonstrated superior effectiveness and improved safety over warfarin in the outpatient management of atrial fibrillation and deep vein thrombosis/pulmonary

embolism [Connolly *et al.* 2010; Schulman *et al.* 2009]. Of the direct factor Xa inhibitors, apixaban has shown greater efficacy over aspirin, and rivaroxaban a better safety profile than warfarin in patients with atrial fibrillation at risk for cardioembolization [Cleland *et al.* 2011; Connolly *et al.* 2011]. Low molecular weight heparin agents, heparinoids and fondaparinux, by inhibiting Xa via antithrombin, have been in use as substitutes for heparin in deep vein thrombosis prophylaxis, or for the treatment of venous thromboembolic disease [Levy *et al.* 2010].

Currently, no medication or transfusion is capable of completely neutralizing the anticoagulant activity of the direct thrombin or (direct or indirect) factor Xa inhibitors, potentially rendering patients with ICH at great risk for continued hemorrhage, hematoma expansion, intraventricular extension, and added morbidity and mortality. In addition to possibly administering oral charcoal to any patient recently ingesting oral anticoagulants [Johnson & Johnson, New Brunswick, NJ; 2009; Van Ryn *et al.* 2009; Bristol Myers Squibb, New York, NY; 2007], empiric transfusion of plasma coagulation products or recombinant coagulation factors may be considered [Van Ryn *et al.* 2010]. Given the more reliable composition of PCCs, and greater concentration of thrombin and factor X, PCCs may be preferred over FFP or rF-VIIa.

Importantly, the pharmacokinetic properties for some of these agents may allow a certain degree of hemostasis and partial control of hemorrhage to be achieved. Specifically, the degree of protein

binding for any given agent may determine the extent to which removal by means of hemodialysis may be feasible and possibly advantageous. Since heparinoids [Pfizer, New York, NY; 2007] hirudin-like agents [Berlex, Montville, NJ; 2004] and dabigatran [Boehringer Ingelheim, Ingelheim, Germany; 2010] possess relatively low or no protein binding, as opposed to other direct or indirect thrombin and factor Xa inhibitors, hemorrhage in conjunction with these agents may theoretically be more likely to respond to serologic extraction by dialysis [Van Ryn *et al.* 2010; Stratmann *et al.* 2004]. Unfortunately, the time required to place central access and administer hemodialysis may prove to be a costly limitation.

Monitoring the anticoagulant activity and effectiveness of reversal for the newer (and older) anticoagulants may be accomplished by measuring anti factor Xa activity for the direct and indirect Xa inhibitors, and by measuring PTT for the direct thrombin inhibitors. Dabigatran may also be monitored using the thrombin time assay, which provides the most linear measure of activity [Boehringer Ingelheim, 2010], and rivaroxaban may be monitored by prothrombin time level but not INR, which is calibrated only for warfarin [Johnson & Johnson, 2009]. Table 1 provides a list of the laboratory tests that may be used to quantify anticoagulation, and the reversal agents for each antithrombotic drug.

Conclusions and future research

Substantial deficiencies persist in evidence-based directives on the management of patients with

Table 1. List of half-life, laboratory tests, and reversal agents for various antithrombotic drugs.

Antithrombotic	T _{1/2}	Lab test	Reversal
Antiplatelets	ASA 2–4 h/24–48 h Clopidogrel 8 h/4–7 days Dipyridamole 10 h/2–4 days	None universally accepted or validated	Platelet transfusion (investigational)
Warfarin	36–48 h	PT/INR	Vitamin K, PCC, FFP, rF-VIIa
Heparin	30–120 min (depending on dose)	PTT	Protamine
LMWH	3–6 h	Anti-Xa activity	Protamine (partially)
Danaparoid	18–28 h	Anti-Xa activity	None
Fondaparinux	18–22 h	Anti-Xa activity	None
Hirudin	60 min	PTT	None
Argatroban	45 min	PTT	None
Dabigatran	12–16 h	PTT/TT	None
Apixaban	8–12 h	Anti-Xa activity	None
Rivaroxaban	8–12 h	PT/anti-Xa activity	None

ASA, aspirin; FFP, fresh frozen plasma; INR, international normalized ratio; LMWH, low molecular weight heparins; PCC, prothrombin complex concentrates; PT, prothrombin time; PTT, partial thromboplastin time; rF-VIIa, recombinant activated factor VII; T_{1/2}, half life; TT, thrombin time.

antithrombotic related ICH. For antiplatelet agents, a standardized and validated method for measuring platelet inhibition from agents with different modes of action is desperately needed, not only for assessing treatment efficacy in preventing vascular thrombotic events [Breet *et al.* 2010], but also for definitively determining whether the degree of antiaggregant activity correlates to ICH expansion [Naidech *et al.* 2009a]. If such a correlation is determined, then randomized trials comparing platelet transfusion to supportive therapy will be needed to conclusively delineate the advantages and/or detriments incurred by transfusion.

Despite theoretical advantages and disadvantages among the various hemotogenous and reconstituted coagulation factor formulations available, sufficient clinical equipoise exists to justify a randomized trial comparing each of the major products, preferably in combination with cobalamin, so as to minimize excessive repeated administrations. Clinical, radiological (hematoma enlargement), and laboratory (INR) outcome measures will be imperative to determine the effectiveness of these therapies, and the reliability of commonly available serological coagulation tests. Documentation of adverse outcomes such as volume overload, immune reactions, infectious complications, and thrombotic events will be equally important.

For the new direct thrombin or factor X inhibitors, research to produce reversing agents is urgently needed given the increasing use of these anticoagulants and the inevitable cerebral and systemic hemorrhages that will ensue. Accurate reporting and comprehensive analysis of postmarketing data for these products is eagerly awaited, and must be compared against available information for the alternative and more traditional therapies, warfarin and aspirin. Subsequent studies to determine the impact of these antidotes in the setting of ICH will then be needed.

For any study of any antithrombotic-reversing modality, optimum quantification of dynamic hematoma evolution must be achieved, possibly by including only supratentorial ICH (or by dividing hemorrhages according to location), by employing computerized methods for comparing initial and subsequent hematoma volumes, and by analyzing final hematoma volume as a continuous and nominal variable (for example, volume

increase >33%). Obtaining information regarding impact upon perihematoma edema or in inducing cerebral ischemia will also be of interest.

Reintroducing antithrombotics after intracerebral hemorrhage

In patients with ischemic cerebrovascular disease, the decision on whether to reinstitute antithrombotic therapy following ICH entails careful consideration of the relative risks for thrombosis *versus* hemorrhage. Risk stratification must be based on the type and severity of ischemic disease, on the underlying cause of ICH, and on the added hemorrhage risk from antithrombosis. Annual risk for recurrent cerebral ischemic events depends on the mechanism involved and the number of coexisting comorbidities, and ranges from 7% to 15% [Sacco *et al.* 2006]. Conversely, the yearly risk of hypertensive ICH recurrence is approximately 2% [Bailey *et al.* 2001] whereas that due to amyloid angiopathy ranges from 5% to 15%, depending on genetic predisposition [O'Donnell *et al.* 2000]. While risk of ICH recurrence does not appear to be increased by aspirin [Viswanathan *et al.* 2006], the risk may be tripled by warfarin [Vermeer *et al.* 2002].

For atrial fibrillation patients with lobar ICH, the risk of recurrent hemorrhage with warfarin may exceed that of embolization [Eckman *et al.* 2003], leading some authorities to recommend antiplatelet agents [Morgensetern *et al.* 2010]. The presence and quantity of microhemorrhages as detected by gradient-echo MRI may indicate and quantify risk for recurrent ICH in such situations, and aid in risk assessment [Fan *et al.* 2003]. The newer oral anticoagulants that carry a lower risk for primary ICH than warfarin (~0.2% *versus* 1% per year) [Hart *et al.* 1995] may impact the decision on whether to restart anticoagulation, but rates of recurrent hemorrhages from these agents have yet to be determined. The timing of antithrombotic reintroduction following ICH is also a topic of uncertainty, with guidelines generally suggesting an abstinence period of 1–2 weeks for antiplatelet agents and 3–4 weeks for oral anticoagulants [Morgensetern *et al.* 2010].

Surgical management

The largest randomized study to assess the role of hematoma evacuation, STICH, enrolled 1033 patients with supratentorial ICH of at least 2 cm to early surgery (median 30 h from onset)

versus medical treatment alone [Mendelow *et al.* 2005]. Patients were eligible if clinical equipoise existed regarding the best treatment strategy, crossover was permitted in the event of neurological deterioration, and method of evacuation was determined by the involved surgeon. In the medical and surgical groups, evacuation was ultimately performed in 94% and 26% of patients, by craniotomy in 85% and 75% of cases, and with 6% needing reevacuation in each group. The primary outcome was functional status at 180 days relative to an admission prognosis score based on age, clinical condition and hematoma size. No differences were observed in favorable outcome from the primary endpoint measure (24% *versus* 26%), or in mortality between the two groups (37% *versus* 36%).

Subgroup analysis from STICH indicated a possible advantage to surgery in patients not in a coma with lobar hemorrhages, and in those with hematomas up to 1 cm from the cortical surface [Mendelow *et al.* 2005]. The ongoing STICH II trial will assess the role of early surgery (<48 h) in patients with lobar ICH less than 1 cm from the cortex surface and no IVH. Limitations to STICH include lack of true randomization given inclusion by the clinical uncertainty principle, inter-institutional variability in determining clinical equipoise, the relatively late timing of surgery, and the large amount of crossover from the medical arm to the surgical group. In a smaller randomized trial of patients with subcortical/deep hemorrhages of at least 30 ml randomized to hematoma removal or medical treatment within 8 h of onset, surgery resulted in improved outcomes for patients not in a coma with hematomas less than 80 ml (33% *versus* 9%), with no difference in mortality [Pantazis *et al.* 2006].

Recently, interest has developed in less invasive stereotactic endoscopic aspiration techniques (variably infusing fibrinolytics), which reduce the likelihood of cerebral injury from surgery. The ongoing MISTIE trial is a dose finding and safety study of intrahematoma tissue plasminogen activator (tPA) infusion in patients with supratentorial ICH greater than 25 ml and symptoms within 72 h. In a related study, CLEAR-IVH will randomize patients with ICH and IVH who present within 24 h with a supratentorial hematoma less than 30 ml to 1–3 mg of tPA or saline via ventriculostomy. Primary endpoints will include mortality and complication rate for MISTIE, and rate of ventricular hemorrhage

resolution for CLEAR-IVH. Finally, despite the absence of trial-based evidence, surgical evacuation is generally recommended for posterior fossa (cerebellar) hematomas that are 3 cm in diameter and causing clinical deterioration, stem compression or obstructive hydrocephalus [Morgensetern *et al.* 2010].

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References

- Almandoz, D., Yoo, A., Stone, M., Schaefer, P., Oleinik, A., Brouwers, H. *et al.* (2010) The spot sign score in primary intracerebral hemorrhage identifies patients at highest risk of in-hospital mortality and poor outcome among survivors. *Stroke* 41: 54–60.
- Anderson, C., Huang, Y., Arima, H., Heeley, E., Skulina, C., Parsons, M. *et al.* (2010) Effects of early intensive blood pressure lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage. *Stroke* 41: 307–312.
- Anderson, C., Huang, Y., Wang, J., Arima, H., Neal, B., Peng, B. *et al.* (2008) Acute Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT). *Lancet Neurology* 7: 391–399.
- Arima, H., Wang, J., Huang, Y., Heeley, E., Skulina, C., Parsons, M. *et al.* (2009) Significance of perihematomal edema in acute intracerebral hemorrhage – the INTERACT Trial. *Neurology* 73: 1963–1968.
- ATACH Investigators. (2010) Antihypertensive treatment of acute cerebral hemorrhage. *Crit Care Med* 38: 637–648.
- Bailey, R., Hart, R., Benavente, O. and Pearce, L. (2001) Recurrent brain hemorrhage is more frequent than ischemic stroke after intracranial hemorrhage. *Neurology* 56: 773–777.
- Barras, C., Tress, B., Christensen, S., MacGregor, L., Collins, M., Desmond, P. *et al.* (2009) Density and shape as CT predictors of intracerebral hemorrhage growth. *Stroke* 40: 1325–1331.
- Berlex (2004) Lepirudin. Montville, NJ; USA.
- Bershad, E. and Suarez, J. (2010) Prothrombin complex concentrates for oral anticoagulant therapy related intracranial hemorrhage – a review of the literature. *Neurocrit Care* 12: 403–414.
- Boehringer Ingelheim (2010) Dabigatran etexilate. Ingelheim, Germany.

- Breet, N., VanWerkum, J., Bouman, H., Kelder, J., Ruven, H., Bal, E. *et al.* (2010) Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA* 303: 754–762.
- Bristol Myers Squibb (2007) Apixaban. New York, NY; USA.
- Broderick, J., Connolly, S., Feldmann, E., Hanley, D., Kase, C., Krieger, D. *et al.* (2007a) Guidelines for the management of spontaneous intracerebral hemorrhage in adults. *Stroke* 38: e391–e413.
- Broderick, J., Diringer, M., Hill, M., Brun, N., Mayer, S., Steiner, T. *et al.* (2007b) Determinants of Intracerebral hemorrhage growth – an exploratory analysis. *Stroke* 38: 1072–1075.
- Brott, T., Broderick, J., Kothari, R., Barsan, W., Tomsick, T., Sauerbeck, L. *et al.* (1997) Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 28: 1–5.
- Carhuapoma, J., Wang, P., Beauchamp, N., Keyl, P., Hanley, D. and Barker, P. (2000) Diffusion-weighted MRI and proton MR spectroscopic imaging in the study of secondary neuronal injury after intracerebral hemorrhage. *Stroke* 31: 726–732.
- Cleland, J., Coletta, A., Buga, L., Antony, R., Pellicori, P., Freemantle, N. *et al.* (2011) Clinical trials update from the American Heart Association Meeting 2010. *Eur J Heart Fail* 13: 460–465.
- Connolly, S., Eikelboom, J., Joyner, C., Diener, H., Hart, R., Golitsyn, S. *et al.* (2011) Apixaban in patients with atrial fibrillation. *N Eng J Med* 364: 806–817.
- Connolly, S., Ezekowitz, M., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A. *et al.* (2010) Dabigatran versus warfarin in patients with atrial fibrillation. *N Eng J Med* 361: 1139–1151.
- Counsell, C., Boonyakarnukul, S., Dennis, M., Sandercock, P., Bamford, J., Burn, J. *et al.* (1995) Primary intracerebral hemorrhage in the Oxfordshire Community Stroke Project. *Cerebrovasc Dis* 5: 26–34.
- Creutzfeldt, C., Weinstein, J., Longstreth, W., Becker, K., McPharlin, T. and Tirschwell, D. (2009) Prior antiplatelet therapy, platelet infusion therapy, and outcome after intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 18: 221–228.
- Cucchiara, B., Messe, S., Sansing, L., Kasner, S. and Lyden, P. (2008) Hematoma growth in oral anticoagulant related intracerebral hemorrhage. *Stroke* 39: 2993–2996.
- Davis, S., Broderick, J., Hennerici, M., Brun, N., Diringer, M., Mayer, S. *et al.* (2006) Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 66: 1175–1181.
- Dickneite, G. (2007) Prothrombin complex concentrate versus recombinant factor viia for reversal of coumarin anticoagulation. *Thromb Res* 119: 643–651.
- Dowlatsahi, D., Demchuk, A., Flaherty, M., Ali, M., Lyden, P. and Smith, E. (2011) Defining hematoma expansion in intracerebral hemorrhage – relationship with patient outcomes. *Neurology* 76: 1238–1244.
- Ducet, A., Hickman, Z., Zacharia, B., Gorobelny, B., DeRosa, P., Landes, E. *et al.* (2010) Impact of platelet transfusion on hematoma expansion in patients receiving antiplatelet agents before intracerebral hemorrhage. *Neurol Res* 32: 706–710.
- Eckman, M., Rosand, J., Knudsen, K., Singer, D. and Greenberg, S. (2003) Can patients be anticoagulated after intracerebral hemorrhage – a decision analysis. *Stroke* 34: 1710–1716.
- Fan, Y., Zhang, L., Lam, W., Mok, V. and Wong, K. (2003) Cerebral microbleeds as a risk factor for subsequent intracerebral hemorrhages among patients with acute ischemic stroke. *Stroke* 34: 2459–2462.
- Fiore, L., Scola, M., Cantillon, C. and Brophy, M. (2001) Anaphylactoid reactions to vitamin K. *J Thromb Thrombolysis* 11: 175–183.
- Flibotte, J., Hagan, N., O'Donnell, J., Greenberg, S. and Rosand, J. (2004) Warfarin, Hematoma Expansion, and Outcome of Intracerebral Hemorrhage. *Neurology* 63: 1059–1064.
- Foerch, C., Sitzler, M., Steinmetz, H. and Neumann-Haefelin, T. (2006) Pretreatment with antiplatelet agents is not independently associated with unfavorable outcome in intracerebral hemorrhage. *Stroke* 37: 2165–2167.
- Gebel, J., Jauch, E., Brott, T., Khoury, J., Sauerbeck, L., Salisbury, S. *et al.* (2002) Relative edema volume is a predictor of outcome in patients with hyperacute spontaneous intracerebral hemorrhage. *Stroke* 33: 2636–2641.
- Gebel, J., Sila, C., Sloan, M., Granger, C., Mahaffy, K., Weisenberger, J. *et al.* (1998) Thrombolysis related intracranial hemorrhage. *Stroke* 29: 563–569.
- Go, A., Hylek, E., Phillips, K., Chang, Y., Henault, L., Selby, J. *et al.* (2001) Prevalence of diagnosed atrial fibrillation in adults. *JAMA* 285: 2370–2375.
- Goldstein, J., Fazen, L., Snider, R., Schwab, K., Greenberg, S., Smith, E. *et al.* (2007) Contrast extravasation on CT angiography predicts hematoma expansion in intracerebral hemorrhage. *Neurology* 68: 889–894.
- Halleivi, H., Albright, K., Aronowski, J., Barreto, A., Schild, S., Khaja, A. *et al.* (2008) Intraventricular hemorrhage – anatomic relationships and clinical implications. *Neurology* 70: 848–852.
- Hart, R., Boop, B. and Anderson, D. (1995) Oral anticoagulants and intracerebral hemorrhage. *Stroke* 26: 1471–1477.
- Hemphill, J., Bonovich, D., Besmertis, L., Manley, G. and Johnston, C. (2001) The ICH score – a simple and reliable grading scale for intracerebral hemorrhage. *Stroke* 32: 891–897.

- Hirsh, J. and Raschke, R. (2004) Heparin and low molecular heparin – the seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126(3 Suppl): 188s–203s.
- Hoff, J. and Xi, G. (2003) Brain edema from intracerebral hemorrhage. *Acta Neurochir* 86(Suppl): 11–15.
- Holland, L. and Brooks, J. (2006) Toward rational fresh frozen plasma transfusion. *Am J Clin Pathol* 126: 133–139.
- Huttner, H., Schellinger, P., Hartmann, M., Kohrmann, M., Juettler, E., Winker, J. *et al.* (2006a) Hematoma growth and outcome in treated neurocritical care patients with intracerebral hemorrhage related to oral anticoagulant therapy. *Stroke* 37: 1465–1470.
- Huttner, H., Steiner, T., Hartmann, M., Kohrmann, M., Juettler, E., Mueller, S. *et al.* (2006b) Comparison of ABC/2 estimation technique to computer assisted planimetric analysis in warfarin related intracerebral parenchymal hemorrhage. *Stroke* 37: 404–408.
- Ichikawa, K. and Yanagihara, C. (1998) Sedimentation level in acute intracerebral hematoma in a patient receiving anticoagulation therapy – an autopsy study. *Neuroradiology* 40: 380–382.
- Isibashi, A., Yokokura, Y. and Adachi, H. (2008) Is antiplatelet therapy for the prevention of ischemic stroke associated with the prognosis of intracerebral hemorrhage?. *Kurume Med J* 55: 71–75.
- Jauch, E., Lindsay, C., Adeoye, O., Khoury, J., Barsan, W., Broderick, J. *et al.* (2006) Lack of evidence for an association between hemodynamic variables and hematoma growth in spontaneous intracerebral hemorrhage. *Stroke* 37: 2061–2065.
- Johnson & Johnson (2009) Rivoroxaban. New Brunswick, NJ; USA.
- Kalita, J., Misra, U., Ranjan, P., Pradhan, P. and Das, B. (2004) Effect of mannitol on regional CBF in patients with intracerebral hemorrhage. *J Neurol Sci* 224: 19–22.
- Kim, J., Kopp, S., Dugan, L. and Diringer, M. (2006) Perihematomal mitochondrial dysfunction after intracerebral hemorrhage. *Stroke* 37: 2457–2462.
- Kollmar, R., Schabitz, W., Heiland, S., Georgiadis, D., Schellinger, P., Bardutzky, J. *et al.* (2002) Neuroprotective effect of delayed moderate hypothermia after focal cerebral ischemia – an MRI study. *Stroke* 33: 1899–1904.
- Kollmar, R., Staykov, D., Dorfler, A., Schellinger, P., Schwab, S. and Bardutzky, J. (2010) Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. *Stroke* 41: 1684–1689.
- Kothari, R., Brott, T., Broderick, J., Barsan, W., Sauerbeck, L., Zuccarello, M. *et al.* (1996) The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 27: 1304–1305.
- Lacut, K., Le Gal, G., Seizeur, R., Prat, G., Mottier, D. and Oger, E. (2007) Antiplatelet drug use preceding the onset of intracerebral hemorrhage is associated with increased mortality. *Fundam Clin Pharmacol* 21: 327–333.
- Lauer, A., Schlunk, F., Van Cott, E., Steinmetz, H., Lo, E. and Foerch, C. (2011) Antiplatelet pretreatment does not increase hematoma volume in experimental intracerebral hemorrhage. *J Cereb Blood Flow Metab* 31: 1736–1742.
- Lee, S., Manno, E., Layton, K. and Wijedicks, E. (2006) Progression of warfarin associated intracerebral hemorrhage after INR normalization with FFP. *Neurology* 67: 1272–1274.
- Leissinger, C., Blatt, P., Hoots, W. and Ewenstein, B. (2008) Role of prothrombin complex concentrates in reversing warfarin anticoagulation – a review of the literature. *Am J Hematol* 83: 137–143.
- Levy, J., Key, N. and Azran, M. (2010) Novel oral anticoagulants – implications in the perioperative setting. *Anesthesiology* 113: 726–745.
- MacLellan, C., Davies, L., Fingas, M. and Colbourne, F. (2006) The influence of hypothermia on outcome after intracerebral hemorrhage in rats. *Stroke* 37: 1266–1270.
- MacLellan, C., Girgis, J. and Colbourne, F. (2004) Delayed onset of prolonged hypothermia improves outcome after intracerebral hemorrhage in rats. *J Cereb Blood Flow Metab* 24: 432–440.
- Makris, M., Greaves, M., Phillips, W., Kitchen, S., Rosendaal, F. and Preston, E. (1997) Emergency oral anticoagulant reversal – the relative efficacy of infusions of fresh frozen plasma and clotting factor concentrate on correction of the coagulopathy. *Thromb Haemost* 77: 477–480.
- Mayer, S., Brun, N., Begtrup, K., Broderick, J., Davis, S., Diringer, M. *et al.* (2005) Recombinant activated factor VII for acute intracerebral hemorrhage. *N Eng J Med* 352: 777–785.
- Mayer, S., Brun, N., Begtrup, K., Broderick, J., Davis, S., Diringer, M. *et al.* (2008) Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Eng J Med* 358: 2127–2137.
- Mayer, S., Davis, S., Skolnick, B., Brun, N., Begtrup, K., Broderick, J. *et al.* (2009) Can a subset of intracerebral hemorrhage patients benefit from hemostatic therapy with recombinant activated factor VII?. *Stroke* 40: 833–840.
- Mendelow, A., Gregson, B., Fernandes, H., Murray, G., Teasdale, G., Hope, D. *et al.* (2005) Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral hematomas in the International Surgical Trial in Intracerebral Hemorrhage (STICH) – a randomized trial. *Lancet* 365: 387–397.

- Misra, U., Kalita, J., Ranjan, P. and Nandal, S. (2005) Mannitol in intracerebral hemorrhage – a randomized controlled study. *J Neurol Sci* 234: 41–45.
- Morgensetern, L., Hemphill, J., Anderson, C., Becker, K., Broderick, J., Connolly, S. *et al.* (2010) Guidelines for the management of spontaneous intracerebral hemorrhage. *Stroke* 41: 2108–2129.
- Moussouttas, M., Malhotra, R., Fernandez, L., Maltenfort, M., Holowecki, M., Delgado, J. *et al.* (2010) Role of antiplatelet agents in hematoma expansion during the acute period of intracerebral hemorrhage. *Neurocrit Care* 12: 24–29.
- Moussouttas, M., Malhotra, R., Fernandez, L., Maltnefort, M., Holowecki, M., Delgado, J. *et al.* (2011) Impact of intraventricular hemorrhage upon intracerebral hematoma expansion. *Neurocrit Care* 14: 50–54.
- Naidech, A., Bassin, S., Bernstein, R., Batjer, H., Alberts, M., Lindholm, P. *et al.* (2009a) Reduced platelet activity is more common than reported antiplatelet medication use in patients with intracerebral hemorrhage. *Neurocrit Care* 11: 307–310.
- Naidech, A., Bernstein, R., Levasseur, K., Bassin, S., Bendok, B., Batjer, H. *et al.* (2009b) Platelet activity and outcome after intracerebral hemorrhage. *Ann Neurol* 65: 352–356.
- Naidech, A.M., Jovanovic, B., Liebling, S., Garg, R.K., Bassin, S.L., Bendok, B.R. *et al.* (2009c) Reduced platelet activity is associated with early clot growth and worse 3-month outcome after intracerebral hemorrhage. *Stroke* 40: 2398–2401.
- O'Donnell, H., Rosand, J., Knudsen, K., Furler, K., Segal, A., Chiu, R. *et al.* (2000) Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. *N Eng J Med* 342: 240–245.
- Olivot, J., Miynash, M., Kleinman, J., Straka, M., Venkatasubramanian, C., Bammer, R. *et al.* (2010) MRI profile of the perihematomal region in acute intracerebral hemorrhage. *Stroke* 41: 2681–2683.
- Pantazis, G., Tsitsopoulos, P., Mihas, C., Katsiva, V., Stavrianos, V. and Zymaris, S. (2006) Early surgical treatment versus conservative management for spontaneous supratentorial intracerebral hematomas – a prospective randomized study. *Surg Neurol* 66: 492–501.
- Pfizer (2007) Dalteparin sodium. New York, NY; USA.
- Polderman, K. and Herold, I. (2009) Therapeutic hypothermia and controlled normothermia in the intensive care unit – practical considerations, side effects and cooling methods. *Crit Care Med* 37: 1101–1120.
- Poungvarin, N., Bhoopat, W., Viriyavejakul, A., Rodprasert, P., Buranasiri, P., Sukondhabhant, S. *et al.* (1987) Effects of dexamethasone in primary supratentorial intracerebral hemorrhage. *N Eng J Med* 316: 1229–1233.
- Qureshi, A., Mendelow, A. and Hanley, D. (2009) Intracerebral hemorrhage. *Lancet* 373: 1632–1644.
- Qureshi, A., Palesch, Y., Martin, R., Novitzke, J., Cruz, S., Ehtisham, A. *et al.* (2010) Effect of systolic blood pressure reduction on hematoma expansion, perihematomal edema, and 3-month outcome among patients with intracerebral hemorrhage. *Arch Neurol* 67: 570–576.
- Raj, G., Kumar, R. and McKinney, W. (1999) Time course of reversal of anticoagulant effect of warfarin by intravenous and subcutaneous phytonadione. *Arch Intern Med* 159: 2721–2724.
- Refaai, M., Phipps, R., Spinelli, S. and Blumberg, N. (2011) Platelet transfusions – impact on hemostasis, thrombosis, inflammation, and clinical outcomes. *Thromb Res* 127: 287–291.
- Roberts, H., Monroe, D. and White, G. (2004) The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 104: 3858–3864.
- Roquer, J., Rodriguez, A., Gomis, M., Ois, A., Puente, V. and Munteis, E. (2005) Previous antiplatelet therapy is an independent predictor of 30-day mortality after spontaneous supratentorial intracerebral hemorrhage. *J Neurol* 252: 412–416.
- Sacco, R., Adams, R., Albers, G., Alberts, M., Benavente, O., Furie, K. *et al.* (2006) Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack. *Stroke* 37: 577–617.
- Saloheimo, P., Ahonen, M., Juvela, S., Pyhtinen, J., Savolainen, E. and Hillbom, M. (2006) Regular aspirin use preceding the onset of primary intracerebral hemorrhage is an independent predictor for death. *Stroke* 37: 129–133.
- Sansing, L., Kaznatcheeva, E., Perkins, C., Komaroff, E., Gutman, F. and Newman, G. (2003) edema after intracerebral hemorrhage – correlations with coagulation parameters and treatment. *J Neurosurg* 98: 985–992.
- Sansing, L., Messe, S., Cucchiara, B., Cohen, S., Lyden, P. and Kasner, S. (2009) Prior antiplatelet use does not affect hemorrhage growth or outcome after ICH. *Neurology* 72: 1397–1402.
- Schulman, S., Kearon, C., Kakkar, A., Mismetti, P., Schellong, S., Eriksson, H. *et al.* (2009) Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Eng J Med* 361: 2342–2352.
- Schwab, S., Georgiadis, D., Berrouschot, J., Schellinger, P., Graffagnino, C. and Mayer, S. (2001) Feasibility and safety of moderate hypothermia after massive hemispheric infarction. *Stroke* 32: 2033–2035.
- Siddique, M., Fernandes, H., Wooldridge, T., Fenwick, J., Slomka, P. and Mendelow, A. (2002) Reversible ischemia around intracerebral hemorrhage – a single photon emission computerized tomography study. *J Neurosurg* 96: 736–741.
- Silva, Y., Leira, R., Tejada, J., Lainez, J., Castillo, J. and Davalos, A. (2005) Molecular signatures of

vascular injury are associated with early growth of intracerebral hemorrhage. *Stroke* 36: 86–91.

Skolnick, B., Mathews, D., Khutoryansky, N., Pusateri, A. and Carr, M. (2010) Exploratory study on the reversal of warfarin with rFVIIa in healthy subjects. *Blood* 116: 693–701.

Sorimachi, T., Fujii, Y., Morita, K. and Tanaka, R. (2007) Predictors of hematoma enlargement in patients with intracerebral hemorrhage treated with rapid administration of antifibrinolytic agents and strict blood pressure control. *J Neurosurg* 106: 250–254.

Steiner, T., Diringer, M., Schneider, D., Mayer, S., Begtrup, K., Broderick, J. *et al.* (2006a) Dynamics of intraventricular hemorrhage in patients with spontaneous intracerebral hemorrhage – risk factors, clinical impact, and effect of hemostatic therapy with recombinant activated factor VII. *Neurosurgery* 59: 767–774.

Steiner, T., Rosand, J. and Diringer, M. (2006b) Intracerebral hemorrhage associated with oral anticoagulant therapy – current practices and unresolved questions. *Stroke* 37: 256–262.

Stratmann, G., DeSilva, A., Tseng, E., Hambleton, J., Balea, M., Romo, A. *et al.* (2004) Reversal of direct thrombin inhibition after cardiopulmonary bypass in a patient with heparin induced thrombocytopenia. *Anesth Analg* 98: 1635–1639.

Sudlow, C. and Warlow, C. (1997) Comparable studies of the incidence of stroke and its pathological types – results from an international collaboration. *Stroke* 28: 491–499.

Tanaka, R., Szlam, F., Dickneite, G. and Levy, J. (2008) Effects of prothrombin complex concentrate and recombinant activated factor VII on vitamin K antagonist induced anticoagulation. *Thromb Res* 122: 117–123.

Tellez, H. and Bauer, R. (1973) Dexamethasone as treatment in cerebrovascular disease – a controlled study in ICH. *Stroke* 4: 541–546.

Toyoda, K., Okada, Y., Minematsu, K., Kamouchi, M., Fujimoto, S., Ibayashi, S. *et al.* (2005) Antiplatelet therapy contributes to acute deterioration of intracerebral hemorrhage. *Neurology* 65: 1000–1004.

Toyoda, K., Yasaka, M., Nagata, K., Nagao, T., Gotoh, J., Sakamoto, T. *et al.* (2009) Antithrombotic

therapy influences location, enlargement, and mortality from intracerebral hemorrhage. *Cerebrovasc Dis* 27: 151–159.

Van Ryn, J., Sieger, P., Kink, M., Gansser, D. and Clemens, A. (2009) Adsorption of dabigatran etexilate in water or dabigatran in pooled human plasma by activated charcoal in vitro [abstract], American Society of Hematology: New Orleans, LA.

Van Ryn, J., Stangier, J., Haertter, S., Liesenfeld, K., Wiene, W., Feuring, M. *et al.* (2010) Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 103: 1116–1127.

Vermeer, S., Algra, A., Franke, C., Koudstaal, P. and Rinkel, G. (2002) Long term prognosis after recovery from primary intracerebral hemorrhage. *Neurology* 59: 205–209.

Vernooij, M., van der Lugt, A., Ikram, M., Wielopolski, P., Niessen, W., Hofman, A. *et al.* (2008) Prevalence and risk factors of cerebral microbleeds – the Rotterdam Study. *Neurology* 70: 1208–1214.

Viswanathan, A., Rakich, S., Engel, C., Snider, R., Rosand, J., Greenberg, S. *et al.* (2006) Antiplatelet use after intracerebral hemorrhage. *Neurology* 66: 206–209.

Wada, R., Aviv, R., Fox, A., Sahlas, D., Gladstone, D., Tomlinson, G. *et al.* (2007) CT angiography spot sign predicts hematoma expansion in acute intracerebral hemorrhage. *Stroke* 38: 1257–1262.

Watson, H., Baglin, T., Laidlaw, S., Makris, M. and Preston, E. (2001) A comparison of the efficacy and rate of response to oral and intravenous vitamin K in reversal of over-anticoagulation with warfarin. *Br J Haematol* 115: 145–149.

Yildiz, O., Arsava, E., Akpınar, E. and Topcuoglu, M. (2011) Previous antiplatelet use is associated with hematoma expansion in patients with spontaneous intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 15, June [epub ahead of print].

Yu, Y., Kumana, C., Lauder, I., Cheung, Y., Chan, F., Kou, M. *et al.* (1992) Treatment of acute cerebral hemorrhage with intravenous glycerol – a double blind placebo controlled randomized trial. *Stroke* 23: 967–971.