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REVIEW

Code-ICH: A New Paradigm for Emergency Intervention

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Abstract

Purpose of review Intracerebral hemorrhage (ICH) is the most devastating type of stroke, causing widespread disability and mortality. Unfortunately, the acute care of ICH has lagged behind that of ischemic stroke. There is an increasing body of evidence supporting the importance of early interventions including aggressive control of blood pressure and reversal of anticoagulation in the initial minutes to hours of presentation. This review highlights scientific evidence behind a new paradigm to care for these patients called Code-ICH.

Recent findings While numerous trials aimed at decreasing hematoma expansion through single interventions had failed to show statistically significant effects on primary outcomes, time-sensitive, multifaceted, bundled care approaches have recently shown substantial promise in improving functional outcomes in patients with ICH.

Summary The concept of Code-ICH can serve as a structural platform for the practice of acute care neurology to continuously measure its performance, reflect on best practices, advance care, and address disparities.

Keywords Intracerebral Hemorrhage · Bundled Care · Neurologic Emergency · Clinical Protocols · Hematoma Expansion · Hemostasis Control

Introduction

"Time is brain" has been a well-recognized mantra in vascular neurology. This is especially evident in the continuously optimized and widely adopted workflow implemented for acute ischemic strokes (AIS). For example, The Joint Commission has championed the use of concrete quality metrics for comprehensive stroke center accreditation, requiring patients presenting with ischemic stroke to have door to needle (tPA) time of 60 min or less and door to arterial puncture time of 90 min or less [1]. Worldwide, the age-standardized mortality rate for AIS has decreased by 33.4% over the period from 1990 to 2017 in part due to improved recognition of symptoms, risk factor modification, advances in reperfusion therapies, and widespread adoption of evidence-based practices [2].

Unfortunately, in contrast, intracerebral hemorrhage (ICH) tends to be treated with less urgency and lacks well-defined, widely adopted time-based quality metrics and treatment protocols. ICH accounts for about 10 to 15% of strokes in high-income countries, whereas in low-to-middle-income countries it accounts for up to half [3]. It has a 40% to 50% mortality rate within 30 days, which is about twice that of ischemic stroke [4]. In a rigorous population-based study, ICH incidence decreased over the decade from 2000 to 2010 in a South Texas community, but case fatality and long-term mortality were unchanged [5]. To make progress in ICH care as a community, this article strongly advocates for a standardized, rigorous, evidence-based new paradigm for emergency intervention for patients presenting with intracerebral hemorrhage. A recent consensus statement puts forth a call to action to establish a protocol for Code ICH [6]. Similarly, new recommendations from the

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American Heart Association similarly advocate for time-based ICH quality metrics [7]. Herein, we review the recent scientific data that enrich our understanding of the urgency of treating ICH in the golden hours after hospital arrival and make the case for the widespread adoption and application of specific time-based quality metrics to provide multidisciplinary patient-centered care for ICH through an innovative platform of Code ICH.

Evidence Behind Strategies to Prevent Hematoma Expansion

One of the most important modifiable factors to improve outcomes in the care of ICH patients is minimizing hematoma expansion. Since the 1990s when IV thrombolytic therapy was investigated for treatment of acute ischemic stroke, it has been well recognized that many patients with ICH experienced expansion of their hemorrhage and deterioration in neurologic function in the first few hours after onset [8]. Studies have described a nonlinear inverse relationship between the time from onset to baseline computed tomography (CT) and expansion risk, with most hematoma expansion noted within 2 to 3 hours of symptom onset [8].

Accordingly, multiple landmark trials have investigated the utility of minimizing hematoma expansion by acutely controlling hypertension. INTERACT-1 (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 1) showed the safety and feasibility of intensive blood pressure control in acute ICH [9]. Subsequently, the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT-2) randomly assigned patients with ICH within previous 6 h and who had elevated blood pressure to receive intensive treatment to lower their blood pressure (with target systolic level of < 140 mmHg within 1 h) or guideline-recommended treatment (with target systolic level of < 180 mmHg). There was no statistically significant difference in death or major disability between the two groups of patients [9]. Similarly, ATACH-II trial (Antihypertensive Treatment of Acute Cerebral Hemorrhage) subsequently found that intensive blood pressure reduction (systolic < 140 mmHg within 4.5 h of onset) did not improve outcome or reduce hematoma expansion compared with standard blood pressure control (systolic range of 140 to 179 mmHg) [10]. As a result, some observers suggested that BP reduction was not an effective strategy.

However, post-hoc analyses of these trials suggested that certain subgroups of patients benefit from earlier treatment to reduce hematoma expansion. For instance, using ATACH-II trial data, Li et. al. analyzed a subgroup of ICH patients with elevated blood pressure treated with intravenous nicardipine within two hours of symptom onset and identified an important association between intensive blood pressure reduction and reduced hematoma growth (odds ratio, 0.56; 95% confidence interval [CI], 0.34–0.92; $p = 0.02$) as well as improved functional outcome as reflected through a favorable shift in 90-day modified Rankin Scale score distribution ($p = 0.04$) [11]. Combining individual patient data from INTERACT-2 and ATACH-2 trials led to an observation that achieving early and stable systolic blood pressure to levels as low as 120 to 130 mmHg was associated with favorable outcomes in patients with mild-to-moderate severity of ICH, but that dramatic drops of more than 60 mmHg to get below 130 mmHg within the first hour were potentially detrimental [12]. Using this data, the 2022 American Heart Association/American Stroke Association (AHA/ASA) guidelines recommended that blood pressure control be initiated as soon as possible and be achieved in a smooth and sustained fashion, preferably titrated using a continuous infusion [13].

More recently, the level of evidence for executing timely blood pressure control in the setting of acute ICH has strengthened beyond post-hoc analyses of existing trials. The Third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT-3) was conducted at hospitals across ten countries examining the impact of early intensive lowering of systolic blood pressure to below 140 mmHg in conjunction with strict glucose control, antipyrexia treatment, and rapid reversal of warfarin-related anticoagulation. Ma et. al. determined that the care bundle protocol implemented within several hours of symptom onset resulted in significantly improved functional outcome in terms of favorable shift in mRS scores and fewer serious adverse events for patients with acute ICH [14]. Much of this effect was driven by blood pressure reduction. As a result, it appears that intensive BP control does in fact improve outcomes, but that the effect is best seen when implemented as one component of a bundle of care. Importantly, the study included an ethnically and socioeconomically diverse population with a large sample size, making its findings more generalizable. Finally, the most recent INTERACT-4 trial found that early BP lowering, when started by EMS within 2 h after symptom onset, specifically improved outcomes in ICH patients, highlighting the value of starting BP reduction as soon as the diagnosis is made [15].

Another important, time-sensitive, and modifiable factor to improve outcomes in patients with acute ICH is hemostatic treatment. Anticoagulant usage has increased in recent years due to our aging population and increased thromboembolic events [16]. Accordingly, the proportion of anticoagulant-associated intracerebral hemorrhage (AAICH) in stroke patients is gradually increasing [17]. The use of anticoagulants is not unexpectedly correlated with larger hematoma volumes, increased rates of hematoma expansion, and even higher mortality rate in patients with AAICH compared with general ICH [18].

Reversal of anticoagulants is central to the care of patients with AAICH. The INCH trial (INR Normalization in Coumadin-Induced Intracerebral Hemorrhage) found that earlier and faster INR normalization was associated with significantly less hematoma expansion and a trend towards lower mortality [19]. Among patients with ICH on factor Xa inhibitors, andexanet was shown to yield better control of hematoma expansion than usual care although there were no significant differences in terms of functional status or death within 30 days [20]. Reversal therapies have become more advanced and targeted over time and are described individually in Table 1. In a recent cohort study involving 9492 patients with anticoagulation-associated ICH and documented reversal intervention status, a total of 7469 (78.7%) received reversal therapy [21]. The median onset-to-treatment time was 232 min and median door-to-treatment time was 82 min, with a door-to-treatment time of 60 min or less in 27.7% of patients [21]. A subgroup analyses found that African American patients and patients admitted to smaller hospitals with lower volume of ICH admissions were less likely to receive timely anticoagulation reversal [21]. Patients with less severe NIHSS score, especially below 5, were also less likely to get reversed early, despite risk for neurologic deterioration and possibly greater opportunity for clinical benefit from anticoagulant therapy reversal [21]. A door-to-treatment time of 60 min or under was associated with decreased mortality and discharge to hospice (adjusted odds ratio, 0.82; 95% CI, 0.69–0.99) but no difference in functional outcome as measured by modified Rankin scale score [21]. These findings as well as the results of INTERACT3 and prior post-hoc analyses indicate that hematoma expansion should be addressed early and more often.

Promise of a Bundled Approach to ICH Care

For many medical conditions, bundled care has been shown to improve outcomes. For instance, the surviving sepsis campaign provided international guidelines for management of sepsis and septic shock, including an hour-1 bundle consisting of five essential elements that should be performed within 60 min of recognizing patients with septic shock. They include obtaining serum lactate, drawing blood cultures prior to antibiotic administration, beginning rapid IV fluid bolus, using vasopressors to keep

Table 1 Reversal therapies currently available for anticoagulant related intracerebral hemorrhage

Anticoagulant type	Specific agent(s)	Reversal agents	Reversal strategy	Lab monitoring	Possible adverse events
Vitamin K antagonists	Warfarin	Vitamin K	10 mg IV	INR	Anaphylaxis
		Fresh Frozen Plasma	4 U or 12 ml/kg IV		Fluid overload
		Prothrombin Complex Concentrate (PCC)	If INR 1.7—4, give 25 U/kg; if INR 4–6, give 35 U/kg; if INR > 6, give 50 U/kg		Thrombotic events
Factor Xa inhibitors	Apixaban Rivaroxaban Edoxaban	Andexanet alfa (preferred drug)	For last intake within 7 h: 800 mg bolus over 30 min. then 960 mg over 2 h For last intake > 7 h: 400 mg bolus over 15 min, then 480 mg over 2 h	Anti-Xa activity	Thrombotic events
		4-factor PCC	50 IU/kg IV (off-label)		Thrombotic events
		Medicinal activated charcoal	50 g if DOAC ingested < 2 h		
Direct Thrombin Inhibitors	Dabigatran	Idarucizumab (preferred drug)	Single 5 g/100 ml dose, repeat if needed	APTT, Thrombin Time	headaches
		Medicinal activated charcoal	50 g if DOAC ingested < 2 h		
Heparinoids	Unfractionated Heparin	Protamine sulfate	1 mg IV for every 100 U of heparin given in the preceding 3 h (up to 50 mg in a single dose)	APTT, anti-Xa activity	Bradycardia, hypotension

Adapted from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11044346/#CR10

mean arterial pressure at least 65 mmHg, and administering broad-spectrum antibiotics [22]. This bundled care approach has been studied in ICH as well by Parry-Jones et al. Implementation of the "ABC" hyperacute care bundle consisting of anticoagulation reversal, intensive blood pressure lowering, neurosurgery consultation, and access to critical care was found to be significantly associated with lower 30-day case fatality after ICH (Odds ratio = 0.62, 95% confidence interval 0.38–0.97, $p = 0.03$) [23]. The total effect of the care bundle was mediated by fewer do-not-resuscitate orders within 24 h and increased admission to critical care [23], highlighting the value of high-quality supportive care rather than any individual intervention. This bundled care approach was further supported by the INTERACT3 trial described in the previous section as well as the Quality in Acute Stroke Care Trial, which included both ischemic stroke and ICH patients and demonstrated that a nursing protocol for managing fever, hyperglycemia, and swallowing dysfunction reduced both disability and death at both 90 days and four years post-intervention [24].

Initiating time-based neuroprotective measures can potentially augment the chances that patients benefit from advances in surgical treatment. The Minimally Invasive Surgery Plus rt-PA for Intracerebral Hemorrhage Evacuation (MISTIE III) trial revealed that minimally invasive surgery (MIS) reduced all-cause mortality, but it did not provide functional outcome benefits at 1-year follow-up [25]. Subgroup analyses suggested that patients who achieved the surgical objective of residual hematoma volume under 15 mL had improved functional outcomes, with an additional 10% increase in the probability of functional independence after one year for each mL of hematoma removed beyond 15 mL ($p = 0.002$) [25]. Polster et al. investigated the post-operative hematoma volume in the MISTIE III and STICH (Surgical Trial in Intracerebral Hemorrhage) I and II trials. Patients who had lower post-operative hematoma volumes had a higher likelihood of an mRS of 0–3 than those who had larger post-operative volumes ($p = 0.01$ in MISTIE III and $p = 0.003$ in STICH II) [26]. Kellner et al. retrospectively reviewed MIS endoscopic ICH evacuation and found that time to evacuation, as well as age, the absence of intraventricular blood, and lobar location were significantly associated with good functional outcomes [27]. A recent multicenter, randomized trial involving patients with acute ICH showed that among patients in whom surgery could be performed within 24 h after the hemorrhage, minimally invasive hematoma evacuation led to better functional outcomes at 180 days than those with guideline-based medical management [28]. While additional studies are needed, this add to the armamentarium of time-sensitive interventions that could make a difference in patients with ICH.

Code-ICH: A Long Overdue Paradigm for Emergency Intervention

Over the years, research and quality improvement measures for patients with ischemic stroke have led to decreases in the median door-to-needle (tPA) time and in-hospital all-cause mortality, and increases the percentage of patients able to be discharged home [29]. The research for similar improvements in outcomes in patients with ICH exists, so it is time for widespread implementation.

This paper highlights the evidence behind treating ICH as a time dependent neurologic emergency and that timely bundled care can make a difference in reducing morbidity and mortality from this condition. The quality of this evidence was most recently reviewed by the AHA/ASA in their guideline for the management of patients with spontaneous intracerebral hemorrhage in 2022 and randomized controlled trials continue to add to the arsenal of data [13].

With a disciplined and data-driven framework, the success with treating ischemic stroke can be readily translated into an improved approach towards ICH care (Fig. 1). Just as in suspected ischemic stroke, patients should be transported to the CT scanner as soon as possible on arrival. When ICH is identified, the Code-ICH team consisting of neurosurgery, neurology, critical care/neurocritical care, emergency medicine, pharmacy, and related disciplines should be mobilized collaboratively, similar to endovascular team activation for large vessel occlusion stroke. Within 60 min of arrival to the ED, hospitals should aim to have performed emergency reversal of anticoagulation for patients on anticoagulation and controlled systolic blood pressure to 130–150 mmHg with the fastest and most effective medications, prioritizing smooth blood pressure control. Any form of anticoagulation should be reversed with the most appropriate available agent with local pharmacy input. Neither the proposed Code-ICH algorithm nor the 2022 AHA/ASA guidelines endorse the administration of any particular reversal agent as a performance measure. With recent advances in electronic medical record technology, ICH order sets should incorporate these elements to streamline decision-making process and facilitate documentation of these emergent interventions in real-time. To continually refine the above algorithm, hospitals should track data on patients with ICH and the efficacy of bundled interventions. By aggregating this valuable data through national and international registries, clinician-researchers will be able to identify system level trends and areas for fine tuning.

This new paradigm for emergency intervention can help address some of the disparities in ICH care. Among patients with primary intracerebral hemorrhage from the National Inpatient Sample (2004–2018), urban (versus rural) hospital patients had a lower likelihood of ICH case fatality (adjusted

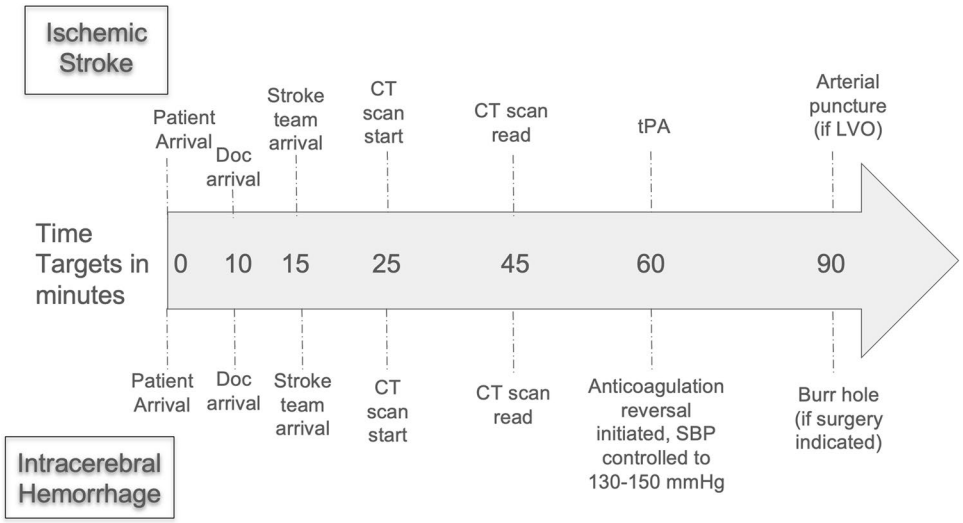

Fig. 1 Time Based Performance Targets for Acute Ischemic Stroke and Proposed Targets for Hemorrhagic Stroke

relative risk 0.86 [95% CI, 0.83–0.89]) [30]. A large prospective multicenter case–control study of ICH among Black patients, Hispanic patients, and White patients observed that Hispanic patients and Black patients arrived to the ED with higher blood pressures compared with White patients and that Black patients continued to be more hypertensive than both Hispanic and White patients 24 h after admission despite more often receiving continuous antihypertensive infusions [31]. By adopting specific and concrete workflows and targets for every patient presenting with ICH regardless of demographic characteristics, opportunities for possible unconscious bias can be minimized. In addition, standardized protocols and training between hub and spoke hospitals, particularly rural settings, can minimize geographic disparities in care.

Because trials supporting urgent intervention for patients with ICH have lagged behind that of AIS, providers, hospitals and organizations have been slower to adopt time-based treatment. One potential barrier to adopting Code-ICH is the pervasive and misinformed nihilism about the outcomes of patients with ICH. Clinicians often hold onto the pessimistic viewpoint that feeds into a self-fulfilling prophecy that ICH patients have poor outcomes, especially those perceived as "frail" on admission, discouraging families from aggressive care right from the beginning, despite the possibility that some of those patients might have had an acceptable outcome if treated more aggressively [32]. Accurately prognosticating after ICH is complex. A recent qualitative study of clinicians' perceptions of the appropriateness of neurocritical care for patients with spontaneous ICH found that participants struggled to balance the concerns of over-treatment against premature treatment withdrawal since patients in the worst prognostic category sometimes surprise their doctors to make a meaningful recovery [33]. Fortunately, consensus statements have emerged in recent years advocating for deferring neuroprognostication—aside from the most clinically devastated patients—for at least the first 48–72 h of intensive care unit admission [34]. In line with this push towards aggressive early care of patients coming in with acute ICH, Code-ICH represents a concrete platform and framework on which to build and implement performance and quality improvement standards for this devastating disease.

Conclusions

Patients presenting with intracerebral hemorrhage deserve to be treated with the same urgency as patients arriving with acute ischemic stroke. The initial minutes to hours have been shown in study after study to be crucial determinants of patient outcomes. By adopting code ICH and pushing for a standardized, time-based, and collaborative approach as outlined in this article, we can excel in maximizing functional recovery for patients with this devastating disease.

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Declarations

Competing interests AY, WY, QL declare that they have no competing interests. SM reports consulting fees from AstraZeneca outside the submitted work. JG reports consulting fees from Astrazeneca, CSL Behring, Octapharma, Cayuga, NControl, and Takeda outside the submitted work.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

References

1. American Heart Association. Phase III Target: Stroke: higher goals for greater good. Accessed May 3, 2024. https://www.heart.org/-/media/files/professional/quality-improvement/target-stroke/target-stroke-phase-iii/ts-phase-iii-5-6-19/final5619-target-stroke-phase-3-brochure.pdf
2. Avan A, Digaleh H, Di Napoli M, Stranges S, Behrouz R, Shojaeianbabaei G, Amiri A, Tabrizi R, Mokhber N, Spence JD, Azarpazhooh MR. Socioeconomic status and stroke incidence, prevalence, mortality, and worldwide burden: an ecological analysis from the Global Burden of Disease Study 2017. BMC Med. 2019;17(1):1–30.
3. Feigin VL, Stark BA, Johnson CO, Roth GA, Bisignano C, Abady GG, Abbasifard M, Abbasi-Kangevari M, Abd-Allah F, Abedi V, Abualhasan A. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Neurology. 2021;20(10):795–820.
4. Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, Gutnikov SA, Edwards P, Mant D, Sackley CM, Farmer A. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). The Lancet. 2004;363(9425):1925–33.
5. Zahuranec DB, Lisabeth LD, Sánchez BN, Smith MA, Brown DL, Garcia NM, Skolarus LE, Meurer WJ, Burke JF, Adelman EE, Morgenstern LB. Intracerebral hemorrhage mortality is not changing despite declining incidence. Neurology. 2014;82(24):2180–6.
6. Li Q, Yakhkind A, Alexandrov AW, Alexandrov AV, Anderson CS, Dowlatshahi D, Frontera JA, Hemphill JC, Ganti L, Kellner C, May C. Code ICH: A Call to Action. Stroke. 2024;55(2):494–505.
7. Ruff IM, de Havenon A, Bergman DL, Dugue R, Frontera JA, Goldstein JN, Hemphill JC, Marulanda-Londono E, Prabhakaran S, Richards CT, Sunmonu NA. 2024 AHA/ASA Performance and Quality Measures for Spontaneous Intracerebral Hemorrhage: A Report From the American Heart Association/American Stroke Association. Stroke. 2024 May 2.
8. Salman RA, Frantzias J, Lee RJ, Lyden PD, Battey TW, Ayres AM, Goldstein JN, Mayer SA, Steiner T, Wang X, Arima H. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. The Lancet Neurology. 2018;17(10):885–94.
9. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368(25):2355–65.
10. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI, Toyoda K. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med. 2016;375(11):1033–43.
11. Li Q, Warren AD, Qureshi AI, Morotti A, Falcone GJ, Sheth KN, Shoamanesh A, Dowlatshahi D, Viswanathan A, Goldstein JN. Ultra-early blood pressure reduction attenuates hematoma growth and improves outcome in intracerebral hemorrhage. Ann Neurol. 2020;88(2):388–95.
12. Moullaali TJ, Wang X, Martin RH, Shipes VB, Robinson TG, Chalmers J, Suarez JI, Qureshi AI, Palesch YY, Anderson CS. Blood pressure control and clinical outcomes in acute intracerebral haemorrhage: a preplanned pooled analysis of individual participant data. Lancet Neurology. 2019;18(9):857–64.
13. Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, Hemphill JC III, Johnson R, Keigher KM, Mack WJ, Mocco J. 2022 Guideline for the management of patients with spontaneous intracerebral hemorrhage: a guideline from the American Heart Association/American Stroke Association. Stroke. 2022;53(7):e282-361.
14. Ma L, Hu X, Song L, Chen X, Ouyang M, Billot L, Li Q, Malavera A, Li X, Muñoz-Venturelli P, de Silva A. The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomised controlled trial. The Lancet. 2023;402(10395):27–40.
15. Li G, Lin Y, Yang J, Anderson CS, Chen C, Liu F, Billot L, Li Q, Chen X, Liu X, Ren X. Intensive ambulance-delivered blood-pressure reduction in hyperacute stroke. New England Journal of Medicine. 2024 May 16.
16. Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, Moomaw CJ, Haverbusch M, Broderick JP. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology. 2007;68(2):116–21.
17. Veltkamp R, Rizos T, Horstmann S. Intracerebral bleeding in patients on antithrombotic agents. InSeminars in thrombosis and hemostasis 2013 Oct 10 (pp. 963–971). Thieme Medical Publishers.
18. Seiffge DJ, Goeldlin MB, Tatlisumak T, Lyrer P, Fischer U, Engelter ST, Werring DJ. Meta-analysis of haematoma volume, haematoma expansion and mortality in intracerebral haemorrhage associated with oral anticoagulant use. J Neurol. 2019;266:3126–35.
19. Steiner T, Poli S, Griebe M, Hüsing J, Hajda J, Freiberger A, Bendszus M, Bösel J, Christensen H, Dohmen C, Hennerici M. Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. Lancet Neurology. 2016;15(6):566–73.
20. Connolly SJ, Sharma M, Cohen AT, Demchuk AM, Członkowska A, Lindgren AG, Molina CA, Bereczki D, Toni D, Seiffge DJ, Tanne D. Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage. N Engl J Med. 2024;390(19):1745–55.
21. Sheth KN, Solomon N, Alhanti B, Messe SR, Xian Y, Bhatt DL, Hemphill JC, Frontera JA, Chang RC, Danelich IM, Huang J. Time to Anticoagulation Reversal and Outcomes After Intracerebral Hemorrhage. JAMA neurology. 2024 Feb 9.
22. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, Mcintyre L, Ostermann M, Prescott HC, Schorr C. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Crit Care Med. 2021;49(11):e1063–143.
23. Parry-Jones AR, Sammut-Powell C, Paroutoglou K, Birleson E, Rowland J, Lee S, Cecchini L, Massyn M, Emsley R, Bray B, Patel H. An intracerebral hemorrhage care bundle is associated with lower case fatality. Ann Neurol. 2019;86(4):495–503.
24. Sridhar D, Ramamoorthy L, Narayan SK, Amalnath D, Lalthanthuami HT, Ganapathy S, Puliyakkuth U. Effectiveness of nurse-led fever, sugar-hyperglycemia, and swallowing bundle care on clinical outcome of patients with stroke at a tertiary care center: A randomized controlled trial. J Neurosci Rural Pract. 2024;15(2):255.
25. Hanley DF, Thompson RE, Rosenblum M, Yenokyan G, Lane K, McBee N, Mayo SW, Bistran-Hall AJ, Gandhi D, Mould WA, Ullman N. Efficacy and safety of minimally invasive surgery with thrombolysis in intracerebral haemorrhage evacuation (MISTIE III): a randomised, controlled, open-label, blinded endpoint phase 3 trial. Lancet. 2019;393(10175):1021–32.

26. Polster SP, Carrión-Penagos J, Lyne SB, Gregson BA, Cao Y, Thompson RE, Stadnik A, Girard R, Money PL, Lane K, McBee N. Intracerebral hemorrhage volume reduction and timing of intervention versus functional benefit and survival in the MISTIE III and STICH trials. Neurosurgery. 2021;88(5):961–70.
27. Kellner CP, Song R, Ali M, Nistal DA, Samarage M, Dangayach NS, Liang J, McNeill I, Zhang X, Bederson JB, Mocco J. Time to evacuation and functional outcome after minimally invasive endoscopic intracerebral hemorrhage evacuation.
28. Pradilla G, Ratcliff JJ, Hall AJ, Saville BR, Allen JW, Paulon G, McGlothlin A, Lewis RJ, Fitzgerald M, Caveney AF, Li XT. Trial of early minimally invasive removal of intracerebral hemorrhage. N Engl J Med. 2024;390(14):1277–89.
29. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Xian Y, Hernandez AF, Peterson ED, Schwamm LH. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. JAMA. 2014;311(16):1632–40.
30. Bako AT, Potter T, Pan A, Tannous J, Rahman O, Langefeld C, Woo D, Britz G, Vahidy FS. Geographic disparities in case fatality and discharge disposition among patients with primary intracerebral hemorrhage. J Am Heart Assoc. 2023;12(10):e027403.
31. Kalasapudi L, Williamson S, Shipper AG, Motta M, Esenwa C, Otite FO, Chaturvedi S, Morris NA. Scoping review of racial, ethnic, and sex disparities in the diagnosis and management of hemorrhagic stroke. Neurology. 2023;101(3):e267–76.
32. Becker KJ, Baxter AB, Cohen WA, Bybee HM, Tirschwell DL, Newell DW, Winn HR, Longstreth WT Jr. Withdrawal of support in intracerebral hemorrhage may lead to self-fulfilling prophecies. Neurology. 2001;56(6):766–72.
33. Mc Lernon S, Werring D, Terry L. Clinicians' perceptions of the appropriateness of neurocritical care for patients with spontaneous intracerebral hemorrhage (ICH): a qualitative study. Neurocrit Care. 2021;35:162–71.
34. Hwang DY, Kim KS, Muehlschlegel S, Wartenberg KE, Rajajee V, Alexander SA, Busl KM, Creutzfeldt CJ, Fontaine GV, Hocker SE, Madzar D. Guidelines for Neuroprognostication in critically ill adults with Intracerebral Hemorrhage. Neurocrit Care. 2024;40(2):395–414.