Neurotherapeutics (2023) 20:705–711
https://doi.org/10.1007/s13311-023-01377-1

REVIEW

# Hemorrhagic Conversion of Acute Ischemic Stroke

**Adeel S. Zubair**[1] · **Kevin N. Sheth**[1,2]

Accepted: 4 April 2023 / Published online: 21 April 2023


**Abstract**
Stroke is a leading cause of morbidity and mortality worldwide; a serious complication of ischemic stroke is hemorrhagic transformation. Current treatment of acute ischemic stroke includes endovascular thrombectomy and thrombolytic therapy. Both of these treatment options are linked with increased risks of hemorrhagic conversion. The diagnosis and timely management of patients with hemorrhagic conversion is critically important to patient outcomes. This review aims to discuss hemorrhagic conversion of acute ischemic stroke including discussion of the pathophysiology, review of risk factors, imaging considerations, and treatment of patients with hemorrhagic conversion.

**Keywords** Acute stroke · Hemorrhagic conversion · Ischemic stroke · Thrombectomy

## Introduction

Ischemic stroke, which is secondary to an arterial occlusion, is a leading cause of morbidity and mortality worldwide and can be caused by a variety of different etiologies [1–3]. One of the serious complications of ischemic stroke is hemorrhagic transformation. Hemorrhagic transformation occurs after acute ischemic stroke (AIS) as well as secondary to venous thrombosis [4, 5]. Studies have reported that hemorrhagic transformation occurs at a rate of between 18 and 42% in acute ischemic stroke [4, 6].

Treatment options for patients who present with acute symptoms concerning for cerebral ischemia include thrombolytic therapy as well as recanalization of the occluded vessel. Alteplase therapy is the current mainstream thrombolytic therapy in patients with ischemic stroke and is associated with a 6 to 8% risk of intracerebral hemorrhage [7–10]. Research shows that less than 5% of ischemic stroke patients benefit from tPA treatment due to the window of treatment and narrow therapeutic window [11]. More recently, many facilities started using tenecteplase (TNK) in place of alteplase for thrombolytic therapy; research from a large, multicenter registry showed decreased rates of symptomatic intracranial hemorrhage when compared to alteplase [12]. Mechanical thrombectomy is the current standard of care in patients with acute ischemia secondary to large vessel occlusion [13]; in 2015, five randomized trials showed the efficacy of endovascular thrombectomy over standard medical care [14–17]. In 2018, two additional trials provided evidence of thrombectomy can be offered up to 24 h after symptom onset in selected group of patients [18, 19]. These therapies come with the risk of subsequent reperfusion injury which can lead to hemorrhagic transformation [20] and is seen to be fatal and roughly 3% of patients treated with acute stroke therapy [10].

Studies have highlighted that more than half of all cerebral infarctions demonstrate certain stages of hemorrhagic transformation [21]. Disruption of the blood–brain barrier within the first hours after ischemia is a thought to be a major player in reperfusion injury as well as subsequent hemorrhagic transformation [22, 23]. Hemorrhagic transformation can be either symptomatic or asymptomatic. Many cases of hemorrhagic transformation, including petechial hemorrhage, are seen to be asymptomatic [24]. Symptomatic intracerebral hemorrhage can often present with rapid neurologic deterioration [25]. After severe hemorrhagic transformation has developed, prognosis for the patient is unfavorable [26–28].

This review aims to discuss hemorrhagic conversion of acute ischemic stroke, specifically in the post-thrombectomy era.

✉ Adeel S. Zubair
Adeel.zubair@yale.edu

[1] Department of Neurology, Yale School of Medicine, New Haven, CT, USA

[2] Division of Neurocritical Care and Emergency Neurology, Yale School of Medicine, New Haven, CT, USA

## Search Strategy

Between August and September of 2022, references for this review were identified by search of PubMed for articles published between 1969 to September of 2022. References from relevant articles were also reviewed. Search terms include acute ischemic stroke, hemorrhagic transformation, stroke, cerebral hemorrhage, ischemic stroke, thrombectomy, and tPA complications. The list of included articles was generated based off of relevance to the topics covered in the review.

## Blood Brain Barrier

The physiologic barrier between the brain parenchyma and brain circulation is called the blood–brain barrier [29, 30]. It is composed of a variety of different cells including pericytes, astrocytes, endothelial cells, and basement membranes; this is collectively referred to as the neurovascular unit [31–33]. Early disruption of this blood–brain barrier is thought to play a central role in hemorrhagic transformation formation in patients with acute ischemic stroke [33, 34].

The blood–brain barrier plays an important role in protecting the brain from different chemicals and has been implicated in a variety of pathologic conditions when impaired [35]. It serves to act as a bidirectional barrier for transport of substances [36, 37]. The blood–brain barrier endothelial cells constitute the luminal component of the blood–brain barrier [38] and allow them to regulate ion movement across the central nervous system [39]. They have increased numbers of mitochondria which allowed them to generate higher amounts of energy in order to augment selective molecular permeability and maintain integrity [38, 40]. Another part of the blood–brain barrier is the junctional complex which comprised gap junctions, tight junctions, and adherens junctions [41, 42]. These play a role in the homeostasis of the blood–brain barrier as well as holding cells together and facilitate intracellular communication [41, 43]. Damage to this area leads to impaired permeability [41].

Many enzymes play a role in the blood–brain barrier. One such enzyme is matrix metalloproteinase-9. Matrix metalloproteinase-9 levels have been associated with hemorrhagic transformation [44]. This is in enzyme which works to degrade endothelial basal lamina and plays an integral role in leading to edema production as well as hemorrhagic transformation [45–47].

There are several stages of damage to the blood–brain barrier; the hyperacute stage (minutes to hours after stroke) occurs after sudden hypoxic damage to the blood–brain barrier, which results in cytotoxic edema and increased permeability, whereas in the acute stage (hours to days), the neuro-inflammatory response aggravates the injury, leading to higher permeability and increased risk of hemorrhagic transformation. This is compounded by reperfusion therapy [35]. With impairment of cerebral blood flow, delivery of oxygen and glucose is compromised, resulting in decreased ATP levels [35]. The subacute stage is typically between 1 and 3 weeks where repair mechanisms are taking place, including neo-angiogenesis. The chronic stage (greater than six weeks) is associated with increase in the blood–brain barrier restoration factors, decreasing permeability [35].

Reopening of the occluded artery in recanalization therapies results in a three-stage process of reperfusion [48, 49]. The first stage is a state of reactive hyperemia with loss of cerebral vaso-regulation which is associated with cytotoxic edema [35]. Following this, there is a stage of hypoperfusion in relation to a reactive microvasculature obstruction that aggravates blood–brain barrier breakdown [35, 49]. This corresponds to a phase of ischemic stunning of the brain [49]. After the hypoperfusion, there is an increase of cellular permeability after initial reperfusion which is associated with vasogenic edema and angiogenesis [49].

Mechanical thrombectomy involves direct endothelial trauma and potential disruption of the blood vessel. The device is used in thrombectomy which can lead to endothelial denudation, edema in the intimal and medial layers, and disruption of the internal elastic lamina [50]. It also results in rapid reperfusion which can be connected with higher levels of hemorrhagic transformation [35]. It has been reported that symptomatic intracranial hemorrhage occurred in 4.4% of patients in the Hermes metanalysis [13].

Research has shown that the non-thrombotic effects of tPA can contribute to hemorrhagic transformation; tPA has been shown to compromise blood–brain barrier integrity via LRP-1 expression on the endothelial cells as well as microglia and astrocytic endfeet [51–53]. It also activates PDGF-cc and kallikrein which promotes BBB disruption [54, 55]. A recent study also showed that immune invasion of the neurovascular unit occurs as a result tPA [56]. Data exists showing that tPA-induced hemorrhagic transformation can occur not only due to reperfusion but through tPA's effect on MMP activity [57].

## Risk Factors of Increased Hemorrhagic Transformation

A variety of clinical features have been associated with increased risk of hemorrhagic transformation in patients with ischemic stroke including strokes severity (NIHSS),

**Table 1** Risk factors for hemorrhagic stroke

| Risk factors for hemorrhagic transformation |
|---|
| Stroke severity (increased NIHSS) |
| Poor collateral blood supply |
| Hyperglycemia |
| Elevated blood pressure |
| Early ischemic changes on imaging |
| Advanced age |
| Low platelet count |
| Use of anti-thrombotic drugs |
| Reperfusion therapy |

hyperglycemia, poor collaterals, hypertension, early infarction on brain imaging, advanced age, low platelet count, use of anti-thrombotic drugs, and reperfusion therapy (Table 1) [58]. One study reported the patient has with NIHSS of greater than 15 had a greater than 50% rate of hemorrhagic transformation [59].

Many of the clinical features associated with risks of increased hemorrhagic transformation are a result of immune system activation and inflammation [60]. Hyperglycemia is also thought to play some role in hemorrhagic transformation and has been shown to increase blood–brain barrier disruption [61]. Two studies, including the GIST UK and SHINE trials, looked at evaluating whether hyperglycemia treatment in the acute setting resulted in better stroke outcomes; both studies did not show significant improvement [62, 63].

Hypertension has been also shown to increase risks of HT. Elevated blood pressure is felt to play a role through a variety of different mechanisms that include exacerbated inflammation, vascular remodeling with effects on collateral and autoregulation, and direct pressure on brain vasculature [64]. It can also lead to disruption of the BBB [60, 65].

Advanced age is also related with increased risk of HT [66, 67]. This risk is multifactorial and is from increased systemic inflammation and changes in the BBB permeability [60]. Elderly patients also have changes in their immune system, including both the adaptive and innate immune system [60, 68].

The direct-MT trial looked that patients who received thrombectomy only versus thrombectomy and alteplase and the rates of hemorrhagic transformation were comparable between the groups [69]. Other studies reported similar rates of hemorrhagic transformation in these two populations [13, 70]. Careful selection of patients with a small core and large penumbra on perfusion imaging for thrombectomy can result in a decreased rate of intracerebral hemorrhage [71]. Other predictors of hemorrhagic transformation after endovascular therapy include low ASPECTS score and poor collateral status [72, 73].

Multiple passes for thrombectomy has also been identified as being associated with a significant increase in blood–brain barrier disruption [74].

## Treatment of Patients with Hemorrhagic Transformation

Treatment of patients with hemorrhagic transformation of acute ischemic stroke is of paramount importance as hemorrhagic transformation is a medical emergency [75]. Most patients with this complication are ready in a healthcare facility, and as such airway, breathing, and cardiovascular support should be available [75]. For patients with hemorrhagic transformation, management changes such as closer attention to blood pressure goals as well as delaying initiation of anti-platelet or anticoagulation therapy should be considered [75]. In patients with hemorrhagic transformation, blood pressure regulation can be controversial and should factor the severity of ICH as well as likelihood of hematoma expansion verses risk of increasing the stroke burden as a secondary complication of hypoperfusion. For patients who had a full recanalization which was then complicated by hemorrhagic transformation, a blood pressure goal of less than 140 mmHg can be considered [75]. Newer research looking into BP target of < 140 mmHg systolic in patients with mild to moderate ischemic stroke with thrombolysis has shown potential benefit [76]. Another recent study showed that while high admission SBP was associated with worse functional outcome after stroke, SBP did not negate the effects of endovascular therapy [77].

The goal of neurosurgical intervention in patients with intracerebral hemorrhage following stroke is to decompress the brain and reduce impact of mass effect and malignant edema [33, 78]. Previous trials looking at decompressive craniotomy in patients with stroke had excluded patients with hemorrhagic transformation (Decimal and Destiny trials); a retrospective study done in Germany highlighted that decompressive craniotomy in patients with hemorrhagic transformation in the setting of malignant cerebral infarction was associated with a worse outcome and higher mortality [79].

## Blood Pressure Management

Blood pressure management and hemodynamics have been felt to be a critical part of post stroke management and thought to play a role in hemorrhagic transformation [80, 81]. Studies have shown high rates of hemorrhagic transformation as well as increased mortality and worse outcomes in patients with higher peak systolic blood pressure values were with hemodynamic variability within the first 24 h after the thrombectomy [81–84]. The current American

Heart guidelines recommend blood pressure goal of less than 180/105 for patients treated with IV thrombolysis or mechanical thrombectomy [85]. This is not supported by randomized clinical trial data however, and the evidence for these recommendations is moderate to weak [80].

The Enchanted trial showed that intensive blood pressure control can potentially reduce the risk of major intracranial hemorrhage in patients with acute ischemic stroke who received IV thrombolytics therapy [86]. Observational studies have highlighted increased risk of hemorrhagic transformation in patients with elevated blood pressure and high blood pressure variability [83]. Blood pressure variability, when elevated, has been considered a risk factor for cerebral edema and post stroke hemorrhagic transformation as this can result in damage to already weak blood vessels [87, 88].

Real-time autoregulation monitoring can help identify dynamic blood pressure range in patients where autoregulation is optimally functioning [89–93]. Cerebral autoregulation is intrinsic capacity of the cerebral vasculature to regulate stable blood flow in the setting of systemic blood pressure changes [94]. This autoregulatory capacity is critical in patients with acute stroke to maintain stable blood flow to the ischemic penumbra and avoid excessive hyper perfusion [80, 95, 96]. Recent studies in this realm have shown that exceeding individualized autoregulatory thresholds was associated with hemorrhagic transformation and worse outcomes [80, 89, 91].

## Imaging Considerations in Hemorrhagic Transformation

The European cooperative acute stroke study (ECASS) has defined the radiographic definition of hemorrhagic transformation [97]. Findings of hemorrhagic transformation on CT scans is divided into 2 stages: hemorrhagic infarction and parenchymal hemorrhage, with or without mass effect. It is important to differentiate between symptomatic and asymptomatic hemorrhage. The SITS-MOST Criteria defines symptomatic intracranial hemorrhage as a local or remote type 2 parenchymal hemorrhage which occurs on the 22-to-36-h post thrombolysis scan and is associated with an increase of NIHSS of 4 points from baseline or leading to death [98, 99].

Other findings on imaging which can mimic hemorrhagic transformation include contrast extravasation after thrombectomy. After thrombectomy, hyper-densities can be seen on post-procedural computed tomography, potentially secondary to intracerebral hemorrhage verses contrast extravasation. These can occur as a result of increased blood–brain barrier permeability or destruction. If contrast is the cause of the hyperdensity, this typically clears up within 24 h and dual energy CT can help distinguish contrast from hemorrhage [100, 101].

### Assessing for Early Stroke

Patients with established stroke is associated with increased risk of hemorrhagic transformation. One way to assess early ischemic changes in adult middle cerebral artery infarction is the Alberta stroke program early CT score (ASPECTS) [102, 103]. The 2019 American Heart Association guidelines suggested use of ASPECTS for patient's presenting within 6 h of onset of large vessel occlusion when determining eligibility for mechanical thrombectomy without perfusion imaging [102, 103].

### Assessment of Blood–Brain Barrier Destruction

Imaging studies have also been done to look at measurement of blood–brain barrier destruction and endothelial damage through CT and MR imaging [104, 105]. The risk study showed that blood–brain barrier leakage was associated with more than a two-fold risk of relevant hemorrhagic transformation and with symptomatic intracerebral hemorrhage [23]. The data showed that pre-treatment blood–brain barrier leakage prior to reperfusion therapy was associated with hemorrhagic transformation which can potentially help identify patients at risk [23].

## Pediatric Populations

It is estimated that childhood ischemic stroke affects 1.2 to 2.4/100 1000 children per year in developed countries [106–110]. Data about hemorrhagic transformation in the pediatric population is limited [111]. One study looked at neuro-imaging for 63 pediatric patients with acute ischemic stroke and found that 30% had evidence of hemorrhagic transformation within thirty days [112]. The majority of these hemorrhages were noted to be petechial with two of them being symptomatic [112]. Causes of increased risk of ischemic stroke hemorrhagic transformation in this study included patients with cardiac conditions and meningitis [112]. Data about endovascular treatment in pediatric patients is very limited. One study looking at 150 Swiss children who presented with acute ischemic stroke between 2000 and 2015 showed that 16 underwent recanalization treatment, of which 6 received endovascular therapy, 5 also received intravenous or intra-arterial thrombolysis [113]. Of this population, 1 child (6.2%) had an asymptomatic ICH and had received intravenous tPA, not mechanical thrombectomy [113].

As discussed above, the ASPECTS score can be used to assess for established stroke. While ASPECTS is not used in pediatric population, a modified pediatric aspect score was evaluated and showed class 2 evidence that it is associated with stroke severity, hemorrhagic transformation, and

12-month outcome in children with acute supratentorial ischemic stroke [102].

## Conclusion

Acute ischemic stroke is widespread global disease which affects millions of people each year. One of the feared complications of AIS is hemorrhagic transformation which can be associated with significant morbidity and mortality. This review aims to discuss hemorrhagic conversion of acute ischemic stroke in the age of thrombectomy. Future studies are needed to help better identify patients at risk and lead to improved outcomes.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s13311-023-01377-1.

**Required Author Forms** Disclosure forms provided by the authors are available with the online version of this article.

## Declarations

**Disclosures** A. S. Z. reports no conflicts of interests related to this work. K. N. S. received grants administered to Yale from Bard, Hyperfine, and Biogen. He received consulting fees from Zoll and Sense for DSMB activities outside the submitted work. He holds equity in Alva and Astrocyte. K. N. S. is supported by NIH R01MD016178, R01EB031114, U24NS107215-04, U24NS107136-05, R01NR018335-04, R01NS110721-04, and R01NS110721-04S1 as well as American Heart Association 17CSA33550004.

## References

1. Zubair AS, Sheth KN. Emergency care of patients with acute ischemic stroke. Neurol Clin. 2021;39(2):391–404.
2. Kamel H, Healey JS. Cardioembolic stroke. Circ Res. 2017;120(3):514–26.
3. Krishnamurthi RV, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health. 2013;1(5):e259–81.
4. Lodder J, Krijne-Kubat B, Broekman J. Cerebral hemorrhagic infarction at autopsy: cardiac embolic cause and the relationship to the cause of death. Stroke. 1986;17(4):626–9.
5. Okada Y, et al. Hemorrhagic transformation in cerebral embolism. Stroke. 1989;20(5):598–603.
6. England TJ, et al. Asymptomatic hemorrhagic transformation of infarction and its relationship with functional outcome and stroke subtype: assessment from the Tinzaparin in Acute Ischaemic Stroke Trial. Stroke. 2010;41(12):2834–9.
7. The National Institute of Neurological Disodrers and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–8. https://doi.org/10.1056/NEJM199512143332401.
8. Benjamin EJ, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56–528.
9. Miller DJ, Simpson JR, Silver B. Safety of thrombolysis in acute ischemic stroke: a review of complications, risk factors, and newer technologies. Neurohospitalist. 2011;1(3):138–47.
10. Whiteley WN, et al. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: a secondary analysis of an individual patient data meta-analysis. Lancet Neurol. 2016;15(9):925–33.
11. Thiebaut AM, et al. The role of plasminogen activators in stroke treatment: fibrinolysis and beyond. Lancet Neurol. 2018;17(12):1121–32.
12 Warach SJ, et al. Abstract 43: Comparative effectiveness of routine tenecteplase thrombolysis in acute stroke compared with alteplase: an INternational Collaboration (CERTAIN Collaboration): rates of symptomatic intracranial hemorrhage. Stroke. 2022;53(Suppl_1):A43–A43.
13. Goyal M, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387(10029):1723–31.
14. Berkhemer OA, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11–20.
15. Goyal M, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372(11):1019–30.
16. Saver JL, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372(24):2285–95.
17. Campbell BC, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372(11):1009–18.
18. Albers GW, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378(8):708–18.
19. Nogueira RG, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378(1):11–21.
20. Balami JS, et al. Neurological complications of acute ischaemic stroke. Lancet Neurol. 2011;10(4):357–71.
21. van Kranendonk KR, et al. Added prognostic value of hemorrhagic transformation quantification in patients with acute ischemic stroke. Front Neurol. 2020;11:582767.
22. Henning EC, et al. Reperfusion-associated hemorrhagic transformation in SHR rats: evidence of symptomatic parenchymal hematoma. Stroke. 2008;39(12):3405–10.
23. Arba F, et al. Blood-brain barrier leakage and hemorrhagic transformation: the Reperfusion Injury in Ischemic StroKe (RISK) study. Eur J Neurol. 2021;28(9):3147–54.
24. Berger C, et al. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? Stroke. 2001;32(6):1330–5.
25. Jensen M, et al. Clinical characteristics and outcome of patients with hemorrhagic transformation after intravenous thrombolysis in the WAKE-UP trial. Front Neurol. 2020;11:957.
26. Iwamoto T, et al. Predicting hemorrhagic transformation after large vessel occlusion stroke in the era of mechanical thrombectomy. PLoS ONE. 2021;16(8):e0256170.
27. Boisseau W, et al. Predictors of parenchymal hematoma after mechanical thrombectomy: a multicenter study. Stroke. 2019;50(9):2364–70.
28. Bardutzky J, Schwab S. Antiedema therapy in ischemic stroke. Stroke. 2007;38(11):3084–94.
29. Kaplan L, Chow BW, Gu C. Neuronal regulation of the blood-brain barrier and neurovascular coupling. Nat Rev Neurosci. 2020;21(8):416–32.
30. Kadry H, Noorani B, Cucullo L. A blood-brain barrier overview on structure, function, impairment, and biomarkers of integrity. Fluids Barriers CNS. 2020;17(1):69.
31. Lochhead JJ, et al. Structure, function, and regulation of the blood-brain barrier tight junction in central nervous system disorders. Front Physiol. 2020;11:914.
32. Bell AH, et al. The neurovascular unit: effects of brain insults during the perinatal period. Front Neurosci. 2019;13:1452.

33. Hong JM, Kim DS, Kim M. Hemorrhagic transformation after ischemic stroke: mechanisms and management. Front Neurol. 2021;12:703258.
34. Arba F, et al. Blood-brain barrier disruption and hemorrhagic transformation in acute ischemic stroke: systematic review and meta-analysis. Front Neurol. 2020;11:594613.
35. Bernardo-Castro S, et al. Pathophysiology of blood-brain barrier permeability throughout the different stages of ischemic stroke and its implication on hemorrhagic transformation and recovery. Front Neurol. 2020;11:594672.
36. Xie J, et al. Nanomaterial-based blood-brain-barrier (BBB) crossing strategies. Biomaterials. 2019;224:119491.
37. Jiang X, et al. Blood-brain barrier dysfunction and recovery after ischemic stroke. Prog Neurobiol. 2018;163–164:144–71.
38. Serlin Y, et al. Anatomy and physiology of the blood-brain barrier. Semin Cell Dev Biol. 2015;38:2–6.
39. Daneman R, Prat A. The blood-brain barrier. Cold Spring Harb Perspect Biol. 2015;7(1): a020412.
40. Blanchette M, Daneman R. Formation and maintenance of the BBB. Mech Dev. 2015;138(Pt 1):8–16.
41. Stamatovic SM, et al. Junctional proteins of the blood-brain barrier: new insights into function and dysfunction. Tissue Barriers. 2016;4(1):e1154641.
42. Rusu AD, Georgiou M. The multifarious regulation of the apical junctional complex. Open Biol. 2020;10(2):190278.
43. Abbott NJ, et al. Structure and function of the blood-brain barrier. Neurobiol Dis. 2010;37(1):13–25.
44. Castellanos M, et al. Serum cellular fibronectin and matrix metalloproteinase-9 as screening biomarkers for the prediction of parenchymal hematoma after thrombolytic therapy in acute ischemic stroke: a multicenter confirmatory study. Stroke. 2007;38(6):1855–9.
45. Castellanos M, et al. Plasma metalloproteinase-9 concentration predicts hemorrhagic transformation in acute ischemic stroke. Stroke. 2003;34(1):40–6.
46. Romanic AM, Madri JA. Extracellular matrix-degrading proteinases in the nervous system. Brain Pathol. 1994;4(2):145–56.
47. Rosenberg GA, et al. Collagenase-induced intracerebral hemorrhage in rats. Stroke. 1990;21(5):801–7.
48. Khatri R, et al. Blood-brain barrier, reperfusion injury, and hemorrhagic transformation in acute ischemic stroke. Neurology. 2012;79(13 Suppl 1):S52–7.
49. Lin L, Wang X, Yu Z. Ischemia-reperfusion injury in the brain: mechanisms and potential therapeutic strategies. Biochem Pharmacol (Los Angel). 2016;5(4).
50. Teng D, et al. Endothelial trauma from mechanical thrombectomy in acute stroke: in vitro live-cell platform with animal validation. Stroke. 2015;46(4):1099–106.
51. Yepes M, et al. Tissue-type plasminogen activator induces opening of the blood-brain barrier via the LDL receptor-related protein. J Clin Invest. 2003;112(10):1533–40.
52. Wang X, et al. Lipoprotein receptor-mediated induction of matrix metalloproteinase by tissue plasminogen activator. Nat Med. 2003;9(10):1313–7.
53. Siao CJ, Tsirka SE. Tissue plasminogen activator mediates microglial activation via its finger domain through annexin II. J Neurosci. 2002;22(9):3352–8.
54. Su EJ, et al. Activation of PDGF-CC by tissue plasminogen activator impairs blood-brain barrier integrity during ischemic stroke. Nat Med. 2008;14(7):731–7.
55. Simão F, et al. Plasma kallikrein mediates brain hemorrhage and edema caused by tissue plasminogen activator therapy in mice after stroke. Blood. 2017;129(16):2280–90.
56. Shi K, et al. tPA mobilizes immune cells that exacerbate hemorrhagic transformation in stroke. Circ Res. 2021;128(1):62–75.
57. Jickling GC, et al. Hemorrhagic transformation after ischemic stroke in animals and humans. J Cereb Blood Flow Metab. 2014;34(2):185–99.
58. Whiteley WN, et al. Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. Stroke. 2012;43(11):2904–9.
59. Kidwell CS, et al. Predictors of hemorrhagic transformation in patients receiving intra-arterial thrombolysis. Stroke. 2002;33(3):717–24.
60. Spronk E, et al. Hemorrhagic transformation in ischemic stroke and the role of inflammation. Front Neurol. 2021;12:661955.
61. Desilles JP, et al. Diabetes mellitus, admission glucose, and outcomes after stroke thrombolysis: a registry and systematic review. Stroke. 2013;44(7):1915–23.
62. Johnston KC, et al. Intensive vs standard treatment of hyperglycemia and functional outcome in patients with acute ischemic stroke: the SHINE randomized clinical trial. JAMA. 2019;322(4):326–35.
63. Gray CS, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). Lancet Neurol. 2007;6(5):397–406.
64. Pires PW, et al. The effects of hypertension on the cerebral circulation. Am J Physiol Heart Circ Physiol. 2013;304(12):H1598–614.
65. Mohammadi MT, Dehghani GA. Acute hypertension induces brain injury and blood-brain barrier disruption through reduction of claudins mRNA expression in rat. Pathol Res Pract. 2014;210(12):985–90.
66. Sohrabji F, Bake S, Lewis DK. Age-related changes in brain support cells: Implications for stroke severity. Neurochem Int. 2013;63(4):291–301.
67. Mazya M, et al. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. Stroke. 2012;43(6):1524–31.
68. Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. Transpl Int. 2009;22(11):1041–50.
69. Yang P, et al. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. N Engl J Med. 2020;382(21):1981–93.
70. Chalos V, et al. Endovascular treatment with or without prior intravenous alteplase for acute ischemic stroke. J Am Heart Assoc. 2019;8(11):e011592.
71. Langel C, Popovic KS. Infarct-core CT perfusion parameters in predicting post-thrombolysis hemorrhagic transformation of acute ischemic stroke. Radiol Oncol. 2018;53(1):25–30.
72. Lee YB, et al. Predictors and impact of hemorrhagic transformations after endovascular thrombectomy in patients with acute large vessel occlusions. J Neurointerv Surg. 2019;11(5):469–73.
73. Nogueira RG, et al. Predictors and clinical relevance of hemorrhagic transformation after endovascular therapy for anterior circulation large vessel occlusion strokes: a multicenter retrospective analysis of 1122 patients. J Neurointerv Surg. 2015;7(1):16–21.
74. Luby M, et al. Frequency of blood-brain barrier disruption post-endovascular therapy and multiple thrombectomy passes in acute ischemic stroke patients. Stroke. 2019;50(8):2241–4.
75. Stone JA, et al. Therapies for hemorrhagic transformation in acute ischemic stroke. Curr Treat Options Neurol. 2017;19(1):1.
76. Chen C, et al. Effects of intensive blood pressure lowering on cerebral ischaemia in thrombolysed patients: insights from the ENCHANTED trial. EClinicalMedicine. 2023;57:101849.
77. Samuels N, et al. Admission systolic blood pressure and effect of endovascular treatment in patients with ischaemic stroke:

an individual patient data meta-analysis. Lancet Neurol. 2023;22(4):312–9.
78. Wang J, et al. Spontaneous cerebellar hemorrhage with severe brainstem dysfunction through minimally invasive puncture treatment by locating the simple bedside. Medicine (Baltimore). 2019;98(38):e17211.
79. Hernández-Durán S, et al. Decompressive craniectomy in malignant stroke after hemorrhagic transformation. Stroke. 2021;52(8):e486–7.
80. Silverman A, et al. Hemodynamics and hemorrhagic transformation after endovascular therapy for ischemic stroke. Front Neurol. 2020;11:728.
81. Mistry EA, et al. Systolic blood pressure within 24 hours after thrombectomy for acute ischemic stroke correlates with outcome. J Am Heart Assoc. 2017;6(5).
82. Goyal N, et al. Blood pressure levels post mechanical thrombectomy and outcomes in large vessel occlusion strokes. Neurology. 2017;89(6):540–7.
83. Kim TJ, et al. Blood pressure variability and hemorrhagic transformation in patients with successful recanalization after endovascular recanalization therapy: a retrospective observational study. Ann Neurol. 2019;85(4):574–81.
84. Malhotra K, et al. Association of blood pressure with outcomes in acute stroke thrombectomy. Hypertension. 2020;75(3):730–9.
85. Powers WJ, et al. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46–110.
86. Anderson CS, et al. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. Lancet. 2019;393(10174):877–88.
87. Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. Stroke. 2008;39(2):366–72.
88. Stead LG, et al. Impact of acute blood pressure variability on ischemic stroke outcome. Neurology. 2006;66(12):1878–81.
89. Petersen NH, et al. Association of personalized blood pressure targets with hemorrhagic transformation and functional outcome after endovascular stroke therapy. JAMA Neurol. 2019;76(10):1256–8.
90. Silverman A, et al. Deviation from personalized blood pressure targets is associated with worse outcome after subarachnoid hemorrhage. Stroke. 2019;50(10):2729–37.
91. Petersen NH, et al. Fixed compared with autoregulation-oriented blood pressure thresholds after mechanical thrombectomy for ischemic stroke. Stroke. 2020;51(3):914–21.
92. Beqiri E, et al. Feasibility of individualised severe traumatic brain injury management using an automated assessment of optimal cerebral perfusion pressure: the COGiTATE phase II study protocol. BMJ Open. 2019;9(9):e030727.
93. Donnelly J, et al. Individualizing thresholds of cerebral perfusion pressure using estimated limits of autoregulation. Crit Care Med. 2017;45(9):1464–71.
94. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Rev. 1990;2(2):161–92.
95. Wang A, Ortega-Gutierrez S, Petersen NH. Autoregulation in the neuro ICU. Curr Treat Options Neurol. 2018;20(6):20.
96. Xiong L, et al. Impaired cerebral autoregulation: measurement and application to stroke. J Neurol Neurosurg Psychiatry. 2017;88(6):520–31.
97. Fiorelli M, et al. Hemorrhagic transformation within 36 hours of a cerebral infarct: relationships with early clinical deterioration and 3-month outcome in the European Cooperative Acute Stroke Study I (ECASS I) cohort. Stroke. 1999;30(11):2280–4.
98. Mac Grory B, et al. Anticoagulation resumption after stroke from atrial fibrillation. Curr Atheroscler Rep. 2019;21(8):29.
99. Külkens S, Hacke W. Thrombolysis with alteplase for acute ischemic stroke: review of SITS-MOST and other Phase IV studies. Expert Rev Neurother. 2007;7(7):783–8.
100. Chen Z, et al. Contrast extravasation is predictive of poor clinical outcomes in patients undergoing endovascular therapy for acute ischemic stroke in the anterior circulation. J Stroke Cerebrovasc Dis. 2020;29(1):104494.
101. Phan CM, et al. Differentiation of hemorrhage from iodinated contrast in different intracranial compartments using dual-energy head CT. AJNR Am J Neuroradiol. 2012;33(6):1088–94.
102. Beslow LA, et al. Association of pediatric ASPECTS and NIH stroke scale, hemorrhagic transformation, and 12-month outcome in children with acute ischemic stroke. Neurology. 2021.
103. Powers WJ, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344–418.
104. Donahue J, Wintermark M. Perfusion CT and acute stroke imaging: foundations, applications, and literature review. J Neuroradiol. 2015;42(1):21–9.
105. Heye AK, et al. Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI. A systematic review. Neuroimage Clin. 2014;6:262–74.
106. Mallick AA, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: a prospective population-based study. Lancet Neurol. 2014;13(1):35–43.
107. Fullerton HJ, et al. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics. 2007;119(3):495–501.
108. Fullerton HJ, et al. Risk of stroke in children: ethnic and gender disparities. Neurology. 2003;61(2):189–94.
109. Grunt S, et al. Cerebral sinus venous thrombosis in Swiss children. Dev Med Child Neurol. 2010;52(12):1145–50.
110. Agrawal N, et al. Imaging data reveal a higher pediatric stroke incidence than prior US estimates. Stroke. 2009;40(11):3415–21.
111. Hutchinson ML, Beslow LA. Hemorrhagic transformation of arterial ischemic and venous stroke in children. Pediatr Neurol. 2019;95:26–33.
112. Beslow LA, et al. Hemorrhagic transformation of childhood arterial ischemic stroke. Stroke. 2011;42(4):941–6.
113. Bigi S, et al. Feasibility, safety, and outcome of recanalization treatment in childhood stroke. Ann Neurol. 2018;83(6):1125–32.