Haemorrhagic transformation in acute ischaemic stroke following thrombolysis therapy: classification, pathogenesis and risk factors

B R Thanvi,[1] S Treadwell,[2] T Robinson[2]

[1] Southwarwickshire Hospital, Warwick, UK; [2] University Hospitals of Leicester NHS Trust, Leicester, UK

Correspondence to: Dr B R Thanvi, Southwarwickshire Hospital, Lakin Road, Warwick CV34 5BW, UK; bthanvi@hotmail.com

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ABSTRACT

Haemorrhagic transformation of cerebral infarction is a common and potentially serious occurrence following acute ischaemic stroke. Though often a "natural" evolution, particularly in acute embolic stroke, haemorrhagic transformation is a prime concern with the use of thrombolytic therapy for acute ischaemic stroke. The severity of haemorrhage may range from a few petechiae to a large haematoma with space occupying effect. The pathogenesis of haemorrhagic transformation is not well established, though ischaemia and reperfusion have been proposed to cause disruption of the blood–brain barrier leading to extravasation of blood. At the molecular level, free radicals and proteolotic enzymes (metalloproteinases) may cause tissue injury. Studies have identified a number of clinical, radiological, and biochemical parameters that may serve as potential predictors of increased risk for haemorrhagic transformation. The knowledge of these factors may help in improving patient selection for thrombolytic therapy.

Cerebral haemorrhage is the most feared complication of thrombolytic therapy for acute ischaemic stroke. Spontaneous haemorrhagic transformation (HT) of infarction is a frequent "natural" evolution, particularly in acute embolic stroke.[1] However, this is often minor and usually does not adversely affect the outcome for the patient. Clinically relevant HT is more common with the thrombolysis and is a major concern with this form of treatment. Most acute stroke trials of thrombolysis have included analysis of the risk of HT. However, there is no uniformity in defining HT in these trials, making it difficult to appraise them. The pathophysiology of HT is not well understood, but recent studies have highlighted the significance of ischaemia and reperfusion injury in the breakdown of permeability barriers leading to the extravasation of blood. Attempts have been made to identify factors that increase the risk of HT, in order to improve patient selection for thrombolytic therapy. In this article, the current knowledge of classifications, pathophysiology, and predictors of HT shall be reviewed.

CLASSIFICATIONS

A haemorrhagic infarction can be defined as an area of bleeding within ischaemic cerebral tissue following an acute ischaemic stroke, and consists pathologically of a large number of red blood cells in addition to leucocytes and macrophages. The extent of the secondary bleed ranges from a few petechiae to large haematomas which may cause substantial pressure effects on the surrounding tissues. Classification of HT can be based upon radiological appearance, or on the presence of associated clinical features which suggest neurological deterioration. Clearly the most relevant question from a clinical point relates to the long term significance of each of these subtypes, and shall be discussed later.

Clinical classification: symptomatic versus asymptomatic

HT is often a natural evolution of ischaemic stroke and is not always symptomatic. Only symptomatic HT may be clinically relevant, though difficulty may arise in defining this. HT is usually attributed to thrombolysis if it occurs within 24–36 h of treatment.

As early as the 1970s, urokinase therapy for the treatment of ischaemic stroke was found to be associated with sudden deterioration and death due to cerebral haemorrhage identified on postmortem studies.[2] In the National Institute of Neurological Disorders and Stroke (NINDS) study,[3] symptomatic haemorrhage was defined as "any CT-documented haemorrhage that was temporally related to deterioration in the patient's condition in the judgement of the clinical investigator". Haemorrhages occurring within 36 h of drug administration were considered to be related to treatment. In the PROACT II (Prolyse in Acute Cerebral Thromboembolism II) study, HT was considered symptomatic when it was associated with an increase in National Institutes of Health Stroke Scale (NIHSS) score of $\geq$4 points within 36 h of treatment initiation.[4] The European Cooperative Acute Stroke Study (ECASS) included radiological (computed tomography (CT)) features in the definition of symptomatic HT by excluding other CT findings which may be responsible for deterioration, along with a worsening of NIHSS by $\geq$4 points.[5] Despite these differences in the definitions, it is generally agreed that symptomatic HT is associated with poor outcomes and mortality rates from 45%[3] to 83%.[4]

The general use of the term "symptomatic haemorrhage" has been criticised by some authors on the basis that the clinical deterioration could result from causes other than HT—for example, ischaemic cerebral oedema and mass effect and a large bleeding into the "silent" areas of the brain may be asymptomatic.[6]

Radiological classification

CT is sensitive at detecting cerebral haemorrhage. Based on the CT appearance, the ECASS group

classified HT into haemorrhagic infarction (HI) and parenchymal haemorrhages (PH).[5] Each class is divided into two types (box 1): HI1 is defined as small petechiae along the margins of the infarct; HI2 as confluent petechiae within the infarcted area but no space occupying effect; PH1 as blood clots in ⩽30% of the infarcted area with space occupying effect; and PH2 as blood clots in >30% of the infarcted area with space occupying effect.

In the NINDS (National Institute of Neurological Disorders and Stroke) study,[3] HT was classified into two types: haemorrhagic cerebral infarction, and intracerebral haematoma. Haemorrhagic cerebral infarction was defined as CT findings of acute infarction with punctate or variable hypodensity and hyperdensity, with an indistinct border within the vascular territory suggested by the acute neurological signs and symptoms. Intracerebral haematoma was defined as CT findings of a typical homogeneous, hyperdense lesion with a sharp border with or without oedema or mass effect within the brain. This hyperdense lesion could arise at a site remote from the vascular territory of the ischaemic stroke or within it, but not necessarily limited to the territory of the presenting cerebral infarction. Haemorrhage with an intraventricular extension was considered an intracerebral haematoma. Clearly, there are differences in the ECASS and NINDS classifications. Whereas space occupying effect is a feature only of PH in the ECASS classification, this is not specific for any of NINDS types. These classifications have important clinical implications, as studies showed that only PH2 (bleed >30% of the infarcted area with space occupying effect) are associated with risk of early neurological deterioration and higher 3 month mortality.[7 8] Applying ECASS criteria, the Canadian Alteplase for Stroke Effectiveness Study (CASES) reported that asymptomatic haemorrhage after thrombolysis may not always be benign and that the likelihood of a poor outcome may be proportional to the extent of haemorrhage on CT scan.[9] Accordingly, HI1 was not related to outcome, though HI2, PH1, and PH2 were all negative predictors.

FREQUENCY OF HAEMORRHAGIC TRANSFORMATION

Haemorrhagic transformation in patients not treated with thrombolysis

HT is a common "natural" evolution following cerebral infarction, and as this is often asymptomatic, difficulty arises in the determination of accurate incidence rates. The rates may also vary depending on the timing of brain imaging, imaging modality used, and prior use of antiplatelet or anticoagulation treatment. In a comparative study of magnetic resonance imaging (MRI) and CT, MRI with echoplanar imaging–gradient–recalled echo sequences had a higher diagnostic accuracy (incidence 48%) in detecting post-stroke HT than did CT (incidence 6–43%).[10]

In a prospective survey by Horning *et al*[11] using clinical and radiological data, HT was reported in 43% of patients with ischaemic stroke. Serial CTs demonstrated that 17% occurred in the first week, 23% in the second week, and 3% in the third week. HT appears to be particularly frequent following cardioembolic stroke. Postmortem series show petechial haemorrhage associated with cerebral infarction in 50–70% of these patients,[12 13] and up to 95% of HT are cardioembolic in origin.[14] Leonard *et al* reported an incidence of 20% HT within 48 h after cardioembolic stroke,[15] and in an angiographic study by Yamaguchi *et al*, the incidence of HT following cardioembolism was 37.5%.[16] Though data for specific subtypes of "natural" HT (for example, symptomatic *vs* asymptomatic and HI vs PH) are limited, those obtained from placebo group analysis in randomised controlled acute stroke trials may provide some insight (table 1); however, the potential for selection and referral bias in these groups should be noted.

Box 1: European Cooperative Acute Stroke Study (ECASS) classification of haemorrhagic transformation[5]

- HI: Petechial infarction without space occupying effect
  - HI1: small petechiae along the margins
  - HI2: confluent petechiae
- PH: Blood clot with space occupying effect
  - PH1: ⩽30% of the infarcted area with space occupying effect
  - PH2: >30% of the infarcted area with space occupying effect

HI, haemorrhagic infarction; PH, parenchymal haemorrhages

Haemorrhagic transformation in patients treated with thrombolysis

The risk of HT associated with thrombolysis therapy is well established. The risk of symptomatic HT in a pooled analysis of six randomised trials was 5.9% in stroke patients treated with recombinant tissue plasminogen activator (rt-PA) compared to 1.1% in control groups.[17] The rates of symptomatic HT are similar for the younger patients and octogenarians.[18–20] It should be noted that asymptomatic petechial HT is statistically independent of thrombolysis, and actually had a reduced incidence in the rt-PA groups compared to controls in ECASS.[5] The risk of HT is also dependent upon the dose, route of administration, timing, and the type of thrombolytic agent used, and this is discussed later when considering the predictors of HT.

PATHOPHYSIOLOGY

The pathophysiology of HT is not fully established and appears to be a complex and dynamic process associated with vascular injury, reperfusion and altered permeability (fig 1). The permeability barriers consist of endothelial cell tight junctions which regulate substrate transfer (the blood–brain barrier), the basal lamina consisting of extracellular matrix proteins that prevents extravasation of cellular blood elements, and perivascular astrocytes which constitute the parenchymal part of the microvasculature.[21] Disruption of the blood–brain permeability barrier with blood extravasation then leads to parenchymal injury through mechanical compression, ischaemia, and toxicity of blood components.[22] It is hypothesised that the loss of microvascular integrity is a prerequisite for the development of HT in focal ischaemia, with or without reperfusion.[21] In the experimental conditions, focal cerebral ischaemia has been shown to cause disruption of microvascular permeability barriers.[23] After occlusion of the middle cerebral artery in primates, alterations in the integrins (adhesion receptors that connect endothelial cells to the components of the underlying basal lamina) and gradual loss of the microvascular basal lamina antigens collagen IV, laminin, and fibronectin have been reported.[23 24]

Fisher and Adams in 1951[14] suggested a role of reperfusion injury. They reported a high incidence of HT following embolic stroke in postmortem studies, and proposed a hypothesis suggesting that HT occurs when an embolus fragments and

Table 1 Rates of haemorrhagic transformation (HT) among placebo groups in randomised controlled trials

	NINDS[34]	ECASS I[7]	ECASS II[17]
Patients, n	312	305	386
Asymptomatic HT	2.9%	29.9%	36.8%
Symptomatic HT	0.6%	6.8%	3.4%

ECASS, European Cooperative Acute Stroke Study; NINDS, National Institute of Neurological Disorders and Stroke.

re-opens a previously occluded vessel, exposing the disrupted endothelium in the infarcted area to reperfusion injury and extravasation of blood. This relationship between re-opening of the occluded vessel and HT is strongly supported by both radiographic and pathologic data.[12 16]

Some patients develop HT without opening of the occluded vessels, and persistent proximal occlusions have been found in 11–17% of HT associated with cardioembolic stroke.[12 16] This has led to a second theory suggesting the role of collateral circulation reperfusion injury. Ogata *et al*[25] indicated that HT may occur with persisting occlusion when infarcted areas are exposed to sufficient perfusion pressure from the leptomeningeal collaterals on the surface of the brain, the mechanism of which has also been demonstrated more recently in animal models.[26]

The role of thrombolysis induced early fibrinogen degradation coagulopathy has been suggested, particularly in the PH types of HT.[27] The early increase in the fibrin degradation products (FDP) has been shown to be a factor contributing to cerebral haemorrhage in thrombolysis for acute myocardial infarction[28] and to the increased risk of PH following thrombolysis with rt-PA in acute ischaemic stroke.[29]

The relative contributions of ischaemic vasculopathy, reperfusion injury, and coagulopathy in various subtypes of HT is unknown, though ischaemia and early reperfusion may be more important in HI whereas ischaemia, coagulopathy, and late reperfusion may be more important in PH types.[27]

Biochemically, there is some evidence that free radical production and activation of matrix metalloproteinases (MMPs) during ischaemia and reperfusion may contribute to the development of HT, and high MMP-9 values have been shown to independently predict HT in patients with and without thrombolysis.[30 31] Though reported to be a promising neuroprotectant in animal models of acute ischaemic stroke, the free radical trapping agent NXY-059 failed to show beneficial effects in terms of mortality and the prevention of alteplase associated haemorrhage in a randomised, placebo controlled, double blind trial.[32]

RISK FACTORS FOR HAEMORRHAGIC TRANSFORMATION

Thrombolysis is the single most effective treatment for acute ischaemic stroke in suitable patients, and it is therefore important to recognise factors which increase the risk of HT in order to improve patient selection and provide appropriate counselling. Factors identified as potential predictors for thrombolysis related HT can be categorised as clinical, biochemical, and radiological features, and these are outlined in table 2.

Clinical predictors

Thrombolytic therapy was associated with a greater risk of PH and symptomatic HT than the placebo treatment in all major acute stroke trials.[17] Symptomatic HT occurs in only 0.6% of patients with ischaemic stroke treated with supportive care,

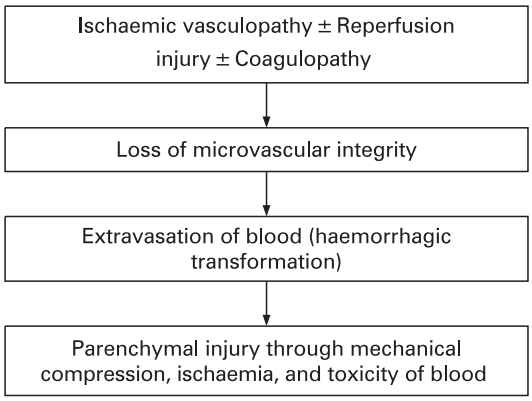

Figure 1 Schema of the pathogenesis of haemorrhagic transformation.

whereas the incidence is higher in those treated with intravenous rt-PA (6%), mechanical embolectomy (8%), and intra-arterial fibrinolytics.[33–35]

Compared with supportive treatment, rt-PA is associated with a greater frequency of PH types than HI types,[7] which may reflect conversion of HI into PH by the thrombolytic agent in a number of cases. Thrombolytic agents may differ in their potential to cause HT. Streptokinase is associated with a significantly greater risk of HT and poor outcome and is not licensed for thrombolysis in acute stroke.[36–38] The increased risk of HT and poor outcome with streptokinase could be related to the prolonged fibrinogen depletion and frequent occurrence of hypotension with this agent.

Currently, rt-PA is the only licensed thrombolytic agent for acute stroke, though newer agents are being evaluated in the research trials. Table 3 compares the rates of HT in patients treated with rt-PA, desmoteplase, and intra-arterial r-prourokinase in acute stroke trials; however, there are no data directly comparing these agents. Comparison of data from different trials is complicated by differences in the size and type of study samples, methodology, definitions of HT, dose, and route of administration. Desmoteplase is a novel, highly fibrin specific thrombolytic agent which was expected to provide better results than rt-PA in acute stroke trials. However, a recently conducted phase IIb/III trial using desmoteplase failed to show any benefit over placebo, and higher doses were associated with a greater frequency of HT and mortality rates.[39] Tenecteplase (TNK) is a modified form of rt-PA, with a longer half-life and greater fibrin specificity, and in doses of 0.1–0.4 mg/kg was found to be safe in a pilot study.[40] Trials are needed to compare the effect of TNK on neurological outcome and safety. Higher doses of lytic agents were associated with an increased risk of HT in DIAS and pilot studies with rt-PA.[41 42] Symptomatic HT occurs at a greater frequency with intra-arterial thrombolysis (10% in PROACT II) than with the intravenous route (6.4% in NINDS), though the baseline median NIHSS score was higher in PROACT II than in NINDS. Rates of HT may be higher for revascularisation with the mechanical devices.[43]

In the pooled analysis of data from six randomised placebo controlled trials of intravenous rt-PA, the time to start of treatment was not associated with an increased risk of HT.[17] In most of the thrombolysis trials, rt-PA was generally given within 3 h of the onset of stroke. In the NINDS trial, there was no difference in the rates of symptomatic HT in patients treated within 90 min and 180 min.[3] However, in the Canadian Alteplase for Stroke Effectiveness Study (CASES), more patients

Table 2 Risk factors for haemorrhagic transformation in acute ischaemic stroke following thrombolysis therapy

Clinical factors	Biochemical markers	Radiological factors
Thrombolytic agent (dose, route of administration, time of onset to thrombolysis, type of agent)	Elevated blood glucose	*Established radiological factors*
	Thrombocytopenia	Early ischaemic change on CT
	Elevated matrix metalloproteinase	Large volume of infarct
Stroke severity	Elevated calcium binding proteins	oedema or mass effect on the baseline CT
Advancing age	Early fibrinogen degradation coagulopathy	*Possible radiological factors*
History of diabetes	Elevated red cell count	Hyperdense artery sign on pre-treatment CT
Elevated blood pressure		Presence of lacunes
Prior use of antithrombotic agents		Reduced blood volume on PWI
History of cardiac failure		Breakdown of blood–brain barrier
History of hyperlipidaemia		Presence of microbleeds on MRI
Increased weight		Leukoariosis on MRI

CT, computed tomography, MRI, magnetic resonance imaging; PWI, perfusion weighted imaging.

with protocol violations treated after 3 h had symptomatic intracranial haemorrhage compared to those treated within guidelines (7.8% *vs* 3.9%).[44] Interestingly, early successful recanalisation has been associated with thrombolysis related HI (HI1-HI2), reduced infarct size and improved clinical outcome,[45] whereas delayed spontaneous recanalisation occurring more than 6 h after acute cardioembolic stroke is an independent predictor of PH and adverse outcome.[46]

Age was found to be an independent risk factor for symptomatic HT in some studies,[17 47] but not in others.[3 7 18 20 48] This discrepancy may be the result of differences in sample size, statistical methods used for analysis, and the differences in the definitions of symptomatic HT. The risk of symptomatic HT in the very old (>80 years of age) is not well studied due to exclusion or under-representation of these patients in most of the studies. In a systematic analysis of six studies of intravenous thrombolysis with rt-PA, Engelter *et al*[19] reported a higher 3 month mortality for patients >80 years of age compared to those <80 years, but the rates of symptomatic HT were similar in both groups. In a study of intra-arterial thrombolysis in ischaemic stroke patients aged ⩾80 years and their younger counterparts, the rates for HT and recanalisation were similar in both groups although outcomes at 90 days showed lower rates of excellent functional outcome (mRS ⩽1, 26% *vs* 40%) and survival (57% *vs* 80%) among the very old.[49] Therefore, risk of HT should not in itself be a reason to exclude older patients from thrombolysis therapy.

Stroke severity has been shown to be a risk factor for HT.[3 5 50] Severity as assessed by NIHSS correlates well with early ischaemic changes on CT[51] and infarction volume on MRI,[52] factors that are also known to be associated with a greater risk of HT.[53 54] The frequency was higher (8.3%) for PH2 than for PH1 (4.2%) in patients with parenchymal hypoattenuation in >33% of the middle cerebral artery territory on baseline CT scan.[47] Conceivably, larger infarcts provide a greater substrate (ischaemic vasculopathy) for HT.

Table 3 Rates of haemorrhagic transformation (HT) in patients treated with thrombolytic agents in the acute stroke trials

	NINDS (rt-PA)	DIAS (low dose desmoteplase)	PROACT II) (r-ProUK)
Patients, n	312	45	108
Asymptomatic HT	4.5%	31.1%	25%
Symptomatic HT	6.5%	2.2%	10%

Blood glucose values and history of diabetes at the time of admission have been recognised as independent risk factors for HT.[4 44 48] Hyperglycaemia and diabetes can cause damage to the microvasculature leading to leakage of oedema fluid and red blood cells.[48]

An acute elevation of blood pressure has been recognised as a risk factor for HT in experimental studies of thrombolysis.[55] Elevated baseline diastolic blood pressure was recognised as a risk factor for HT in the pilot phases of the NINDS rt-PA study.[56 57] High blood pressure has also been associated with increased risk of intracerebral haemorrhage following thrombolysis for myocardial infarction.[58] However, in a systematic review of studies using multivariate analyses to identify independent risk factors for symptomatic HT with thrombolysis, Lansberg *et al*[59] recognised only one study[60] that reported blood pressure as an independent risk factor. As blood pressure levels above certain levels are considered exclusion criteria for thrombolysis, the precise role of hypertension as a predictor for HT may never be established.

Prior use of aspirin has been associated with an increased risk of HT in patients treated with thrombolysis.[42 47 61] In the secondary analysis of the ECASS-II, the odds ratios for PH were 3.6 for rt-PA, 1.26 for aspirin, and 4.99 for rt-PA plus aspirin.[47] Negative interaction of aspirin has also been noted with streptokinase therapy in acute stroke,[62] though aspirin was not associated with greater risk of HT in ECASS and NINDS trials.[3 5]

In the secondary analysis of ECASS data, a history of cardiac failure (but not atrial fibrillation or myocardial infarction) was associated with an increased risk (odds ratio 2.57) of PH.[47] The authors consider ventricular thrombus as a potential mechanism of cerebral embolism in these patients, though this association has not been studied elsewhere. History of hyperlipidaemia and weight were risk factors in univariate but not in multivariate analysis of predictors for HT.[63]

Laboratory predictors

The association of blood glucose values and HT has already been alluded to.

Thrombocytopenia is a risk factor for HT following thrombolysis for ischaemic stroke. Platelet counts lower than 100 000/μl are therefore a contraindication for thrombolysis therapy. The lower baseline platelet counts have been reported as independent risk factors for HT,[48] though this has not been confirmed in other studies.[4 47]

Thrombolysis induced early fibrinogen degradation coagulopathy has been shown to predict risk of PH types of HT.[27] The

Box 2: Some of the questions for future research in stroke thrombolysis

- What is the relative significance of ischaemia, reperfusion, and early fibrin degradation coagulopathy in the pathogenesis of subtypes of haemorrhagic transformation (HT)?
- Is fibrin specificity the major discriminant for the potential to cause HT among the thrombolytic agents?
- What is the role of biochemical markers such as matrix metalloproteases and calcium binding protein S100B in predicting risk of HT?
- What is the precise role of newly recognised magnetic resonance imaging markers, such as decreased cerebral blood volume on perfusion weighted imaging, hyperintense acute reperfusion marker (HARM), and evidence of the disruption of the blood–brain barrier in predicting HT risk?

risk of HT is higher in patients on anticoagulation therapy and the risk increases with the dose.[64] In patients who are not on anticoagulants, the baseline procoagulant or profibrinolytic states may influence the risk of HI with thrombolysis. Low level of plasminogen activator inhibitor (PAI-I) is found to be a risk factor for HT in one[65] but not in another study.[50] Elevated red cell count has also been suggested as a risk factor for HT in one study.[63]

The levels of matrix metalloproteinases (MMPs), a family of zinc binding proteolytic enzymes that normally remodel the extracellular matrix, relate to blood–brain barrier disruption after cerebral ischaemia.[31] High pre-treatment levels of MMP-9 have been associated with an increased risk of PH.[31] Elevated values of a calcium binding protein, S100B (a marker of disruption of the blood–brain barrier), has been shown to be an independent risk factor for HT.[66] In a multicentre study of rt-PA, none of the haemostatic markers (fibrinogen, prothrombin fragments, factor VII, factor XIII, antiplasmins, and PAI-I) were associated with an increased risk of HT.[50]

Radiological predictors

Early ischaemic changes on CT have been associated with an increased risk of HT in several studies.[3 48 53 67] These changes include hypodensity of brain parenchyma, loss of grey–white differentiation, effacement of sulci, and compression of ventricles. The extent of change tends to correlate with the risk of HT. A threefold increase in the risk of symptomatic HT was noted in patients with early infarct size of less than a third of the middle cerebral artery (MCA) territory, and the risk increased by sixfold in those with changes affecting more than a third.[48] Similar results were noted in ECASS I.[68] Evidence of oedema or mass effect on the baseline CT was significantly associated with an increased risk of symptomatic HT during the first 36 h after start of treatment in NINDS.[3]

Recently, there has been increasing interest in the use of MRI, with a particular hope of extending the time of onset to thrombolysis beyond the usual 3 h window. Presence of lacunes on MRI was noted to predict HT.[63] A large volume of infarct on the diffusion weighted scan is shown to be an independent risk factor for HT.[69] This was confirmed in a recent multicentre study of symptomatic HT with thrombolysis.[49] The patients were categorised according to the pre-treatment DWI lesion size into three pre-specified groups: small ($\leqslant$10 ml), moderate (10–100 ml), and large (>100 ml) DWI lesions.[49] The incidence of symptomatic HT significantly differed between subgroups: 2.8%, 7.8%, and 16.1% in patients with small, moderate, and large DWI lesions, respectively. Patients with a pre-treatment hyperdense middle cerebral artery sign on CT showed larger volume lesions on perfusion and diffusion weighted MRI and were associated with an increased risk of HT and death.[63] Other putative predictors of increased risk include low cerebral blood volume on perfusion weighted imaging,[70] hyperintense acute reperfusion marker (HARM) as evidenced by a delayed gadolinium enhancement of cerebrospinal fluid space on FLAIR sequences,[71] and evidence of disruption of the blood–brain barrier in the form of enhancement on post-contrast T-1 weighted images.[72] The initial suggestion of cerebral microbleeds as detected on pre-treatment gradient echo MRI as predictors of HT has not been confirmed in recent studies.[73–75] Presence of leukoariosis on MRI is considered to be an important risk factor for HT.[76]

PROGNOSIS

Parenchymal haemorrhage after thrombolysis is associated with a higher mortality and worse outcome in surviving patients.[8 47] However, asymptomatic HT is common and thought to be a natural evolution of reperfusion into ischaemic tissue without any clinical impact.[6 77] HI defined by ECASS criteria has no significant impact on the outcome at 3 months in ECASS 1 and ECASS 2 studies.[7 47] HI is statistically independent of rt-PA treatment, and actually has a lower incidence in rt-PA groups than control groups in ECASS 1 and ECASS 2.[5 47]

Symptomatic HT was associated with mortality rates of 45% in NINDS,[34] and 83% in PROACT-2.[33] In NINDS part 2, mortality associated with symptomatic haemorrhage was increased by a 10-fold factor in the rt-PA group (47%) when compared with the placebo group (4.7%).[3 34] However, the overall mortality was decreased in the rt-PA group (17% *vs* 21%) because of the reduction in non-haemorrhagic deaths, and even subgroups at the highest risk for HT show a net benefit of rt-PA treatment within 3 h.

SUMMARY

Thrombolytic therapy in acute ischaemic stroke is associated with a significant risk of HT and there has been an increasing interest in identifying factors that may predict this risk. Not all forms of HT have an adverse effect on patient outcomes and the efforts should be directed towards identifying subtypes of HT that are clinically relevant. Though clinical and radiological

Key points

- Haemorrhagic transformation (HT) of cerebral infarction is a common and potentially serious occurrence following acute ischaemic stroke.
- HT is frequently seen as a "natural" evolution in ischaemic infarction but is often asymptomatic.
- Compared to placebo treatment, thrombolytic therapy greatly increases the risk of symptomatic HT.
- The main predictors of clinically significant HT are age, clinical stroke severity, high blood pressure, hyperglycaemia, early computed tomography changes, and large baseline diffusion lesion volume on magnetic resonance imaging.
- The pathogenesis of haemorrhagic transformation is not well understood, though ischaemia and reperfusion have been implicated in the disruption of the blood–brain barrier leading to extravasation of blood.

classifications serve as a useful guide to the severity of HT, both have limitations. The pathogenesis of HT is becoming increasingly clear with improved understanding of the mechanisms involved with the breakdown of permeability barriers at a molecular level. In a recently published study, early disruption of barrier caused by focal cerebral ischaemia in human stroke was assessed by the presence of gadolinium enhancement of cerebrospinal fluid, termed ''hyperintense acute injury marker'' (HARM).[78] This was found to be an independent predictor of HT.

Most of the current research in stroke thrombolysis exploits advances in brain imaging in the hope of identifying better predictors of HT, and extending the window for thrombolysis. Despite these advances, several questions remain unanswered (box 2). The search for an ideal thrombolytic agent continues, though it should be remembered that thrombolysis is the single most effective treatment for acute ischaemic stroke, and even patients at high risk for HT based on factors identified so far show an overall net benefit due to the reduction in non-haemorrhagic deaths. Future studies may reveal additional information in this area so that patient selection for thrombolysis can be further improved, and potential complications of thrombolytic therapy minimised.

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REFERENCES

1. **Teal PA,** Pessin MS. Hemorrhagic transformation. The spectrum of ischemia-related brain hemorrhage. *Neurosurg Clin N Am* 1992;**3**:601–10.
2. **Hanaway J,** Torack R, Fletcher AP, *et al*. Intracranial bleeding associated with urokinase therapy for acute ischaemic hemispherical stroke. *Stroke* 1976;**7**:143–146.
3. **The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group**. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke* 1997;**28**:2109–18.
4. **Kase CS,** Furlan AJ, Wechsler LR, *et al*. Cerebral haemorrhage after intra-arterial thrombolysis for ischemic stroke: the PROACT II trial. *Neurology* 2001;**57**:1603–10.
5. **Larrue V,** von Kummer R, del Zoppo G, *et al*. Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European Cooperative Acute Stroke Study. *Stroke* 1997;**28**:957–60.
6. **von Kummar R.** Brain haemorrhage after thrombolysis: good or bad? *Stroke* 2002;**33**:1446–7.
7. **Fiorelli M,** Bastianello S, von Kummer R, *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**:2280–4.
8. **Berger C,** Fiorelli M, Steiner T, *et al*. Hemorrhagic transformation of ischemic brain tissue: asymptomatic or symptomatic? *Stroke* 2001;**32**:1330–5.
9. **Libman R,** Kwiatkowski T. Asymptomatic hemorrhage after thrombolysis may not be benign: prognosis by hemorrhage type of the Canadian alteplase for stroke effectiveness study registry. *Stroke* 2007;**38**:e88.
10. **Arnould MC,** Grandin CB, Peeters A, *et al*. Comparison of CT and three MR sequences for detecting and categorizing early (48 hours) hemorrhagic transformation in hyperacute ischemic stroke. *Am J Neuroradiol* 2004;**25**:939–44.
11. **Hornig CR,** Dorndorf W, Agnoli AL. Haemorrhagic cerebral infarction – a prospective study. *Stroke* 1986;**17**:179–85.
12. **Jorgensen L,** Torvik A. Ischaemic cerebrovascular diseases in an autopsy series, 2: prevalence, location, pathogenesis, and clinical course of cerebral infarcts. *J Neurol Sci* 1969;**9**:285–320.
13. **Pessin MS,** Del Zoppo GJ, Estol CJ. Thrombolytic agents in the treatment of stroke. *Clin Neuropharmacol* 1990;**13**:271–89.
14. **Fisher CM,** Adams RD. Observations on brain embolism with special reference to the mechanism of haemorrhagic infarction. *J Neuropath Exp Neurol* 1951;**10**:92–3.
15. **Leonard AD,** Newburg S. Cardioembolic stroke. *J Neurosci Nurs* 1992;**24**:69–76.
16. **Yamaguchi T,** Minematsu K, Choki JI, *et al*. Clinical and neuroradiological analysis of thrombotic and embolic cerebral function. *Jap Circ J* 1984;**48**:50–8.
17. **Hacke W,** Donnan G, Fieschi C, *et al*. ATLANTIS Trials Investigators, ECASS Trials Investigators, NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* 2004;**363**:768–74.
18. **Ringleb PA,** Schwark C, Kohrmann M, *et al*. Thrombolytic therapy for acute ischaemic stroke in octogenarians: selection by magnetic resonance imaging improves safety but does not improve outcome. *J Neurol Neurosurg Psychiatry* 2007;**78**:690–3.
19. **Engelter ST,** Bonati LH, Lyrer PA. Intravenous thrombolysis in stroke patients of > or = 80 versus <80 years of age – a systematic review across cohort studies. *Age Ageing* 2006;**35**:572–80.
20. **Berrouschot J,** Rother J, Glahn J, *et al*. Outcome and severe hemorrhagic complications of intravenous thrombolysis with tissue plasminogen activator in very old (> or = 80 years) stroke patients. *Stroke* 2005;**36**:2421–5.
21. **del Zoppo GJ,** von Kummer R, Hamann GF. Ischaemic damage of brain microvessels: inherent risks for thrombolytic treatment in stroke. *J Neurol Neurosurg Psychiatry* 1998;**65**:1–9.
22. **Wang X,** Lo EH. Triggers and mediators of haemorrhagic transformation in cerebral ischaemia. *Mol Neurobiol* 2003;**28**:229–44.
23. **Burggraf D,** Trinkl A, Burk J, *et al*. Vascular integrin immunoreactivity is selectively lost on capillaries during rat focal cerebral ischemia and reperfusion. *Brain Res* 2008;**1189**:189–97.
24. **Wagner S,** Tagaya M, Koziol JA, *et al*. Rapid disruption of an astrocyte interaction with the extracellular matrix mediated by integrin alpha 6 beta 4 during focal cerebral ischemia/reperfusion. *Stroke* 1997;**28**:858–65.
25. **Ogata J,** Yutani C, Imakita M, *et al*. Haemorrhagic infarct of the brain without a reopening of the occluded arteries in cardioembolic stroke. *Stroke* 1989;**20**:876–83.
26. **Saku Y,** Choki J, Waki R, *et al*. Haemorrhagic infarct induced by arterial hypertension in cat brain following middle cerebral artery occlusion. *Stroke* 1990;**21**:589–95.
27. **Trouillas P,** von Kummer R. Classification and pathogenesis of cerebral hemorrhages after thrombolysis in ischemic stroke. *Stroke* 2006;**37**:556–61.
28. **Kase CK,** Pessin MS, Zivin JA, *et al*. Intracranial hemorrhage after coronary thrombolysis with tissue plasminogen activator. *JAMA* 1992;**92**:384–90.
29. **Trouillas P,** Derex L, Philippeau F, *et al*. Early fibrinogen degradation coagulopathy is predictive of parenchymal hematomas in cerebral rt-PA thrombolysis: a study of 157 cases. *Stroke* 2004;**35**:1323–8.
30. **Castellanos M,** Leira R, Serena J, *et al*. Plasma metalloproteinase-9 concentration predicts haemorrhagic transformation in acute ischaemic stroke. *Stroke* 2003;**34**:40–6.
31. **Montaner J,** Molina CA, Monasterio J, *et al*. Matrix metalloproteinase-9 pretreatment level predicts intracranial hemorrhagic complications after thrombolysis in human stroke. *Circulation* 2003;**107**:598–603.
32. **Shuaib A,** Lees KR, Lyden P, *et al*, SAINT II Trial Investigators. NXY-059 for the treatment of acute ischemic stroke. *N Engl J Med* 2007;**357**:562–71.
33. **Furlan A,** Higashida R, Wechsler L, *et al*. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA* 1999;**282**:2003–11.
34. **The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group**. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;**333**:1581–7.
35. **Smith WS,** Sung G, Starkman S, *et al*. MERCI Trial Investigators. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke* 2005;**36**:1432–8.
36. **Multicenter Acute Stroke Trial-Europe Study Group**. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med* 1996;**335**:145–50.
37. **Morris AD,** Ritchie C, Grosset DG, *et al*. A pilot study of streptokinase for acute cerebral infarction. *Q J M* 1995;**88**:727–31.
38. **Donnan GA,** Davis SM, Chambers BR, *et al*, for the Australian Streptokinase (ASK) Trial Study Group. Streptokinase for acute ischemic stroke with relationship to time of administration. *JAMA* 1996;**276**:961–6.
39. **The Internet Stroke Centre**. DIAS-2 desmoteplase in acute ischemic stroke. http://www.Strokecenter.Org/trials/trialdetail.Aspx?Tid = 515, 2007.
40. **Haley EC Jr,** Lyden PD, Johnston KC, *et al*, TNK in Stroke Investigators. A pilot dose-escalation safety study of tenecteplase in acute ischemic stroke. *Stroke* 2005;**36**:607–12.
41. **Hacke W,** Albers G, Al-Rawi Y, *et al*, DIAS Study Group. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke* 2005;**36**:66–73.
42. **Levy DE,** Brott TG, Haley EC Jr, *et al*. Factors related to intracranial hematoma formation in patients receiving tissue-type plasminogen activator for acute ischemic stroke. *Stroke* 1994;**25**:291–7.
43. **Smith WS.** Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke. Results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. *AJNR Am J Neuroradiol* 2006;**27**:1177–82.
44. **Hill MD,** Buchan AM, Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *Can Med Assoc J* 2005;**172**:1307–12.
45. **Molina CA,** Alvarez-Sabín J, Montaner J, *et al*. Thrombolysis-related hemorrhagic infarction: a marker of early reperfusion, reduced infarct size, and improved outcome in patients with proximal middle cerebral artery occlusion. *Stroke* 2002;**33**:1551–6.
46. **Molina CA,** Montaner J, Abilleira S. Timing of spontaneous recanalization and risk of hemorrhagic transformation in acute cardioembolic stroke. *Stroke* 2001;**32**:1079–84.
47. **Larrue V,** von Kummer RR, Müller A, *et al*. Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). *Stroke* 2001;**32**:438–41.
48. **Tanne D,** Kasner SE, Demchuk AM, *et al*. Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. *Circulation* 2002;**105**:1679–85.
49. **Kim D,** Ford GA, Kidwell CS, *et al*. UCLA Intra-Arterial Thrombolysis Investigators. Intra-arterial thrombolysis for acute stroke in patients 80 and older: a comparison of results in patients younger than 80 years. *AJNR Am J Neuroradiol* 2007;**28**:159–63.
50. **Cocho D,** Borrell M, Martí-Fàbregas J, *et al*. Pretreatment hemostatic markers of symptomatic intracerebral hemorrhage in patients treated with tissue plasminogen activator. *Stroke* 2006;**37**:996–9.

51. **Patel SC,** Levine SR, Tilley BC, *et al*. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *JAMA* 2001;**286**:2830–8.
52. **Tong DC,** Yenari MA, Albers GW, *et al*. Correlation of perfusion- and diffusion-weighted MRI with NIHSS score in acute (<6.5 hour) ischemic stroke. *Neurology* 1998;**50**:864–70.
53. **Jaillard A,** Cornu C, Durieux A, *et al*. Hemorrhagic transformation in acute ischemic stroke. The MAST-E study. *Stroke* 1999;**30**:1326–32.
54. **Kakuda W,** Thijs VN, Lansberg MG, *et al*. DEFUSE Investigators. Clinical importance of microbleeds in patients receiving IV thrombolysis. *Neurology* 2005;**65**:1175–8.
55. **Bowes MP,** Zivin JA, Thomas GR, *et al*. Acute hypertension, but not thrombolysis, increases the incidence and severity of hemorrhagic transformation following experimental stroke in rabbits. *Exp Neurol* 1996;**141**:40–6.
56. **Brott TC,** Haley EC, Levy DE, *et al*. Urgent therapy for stroke, part I: pilot study of tissue plasminogen activator administered within 90 minutes from onset. *Stroke* 1992;**23**:632–40.
57. **Haley EC,** Levy DE, Brott TC, *et al*. Urgent therapy for stroke, part II: pilot study of tissue plasminogen activator administered within 90–180 minutes from onset. *Stroke* 1992;**23**:641–5.
58. **Gore JM,** Granger CB, Simoons ML, *et al*. Stroke after thrombolysis. Mortality and functional outcomes in the GUSTO-I trial. Global Use of Strategies to Open Occluded Coronary Arteries. *Circulation* 1995;**92**:2811–8.
59. **Lansberg MG,** Albers GW, Wijman CA. Symptomatic intracerebral hemorrhage following thrombolytic therapy for acute ischemic stroke: a review of the risk factors. *Cerebrovasc Dis* 2007;**24**:1–10.
60. **Gilligan AK,** Markus R, Read S, *et al*. Australian Streptokinase Trial Investigators. Baseline blood pressure but not early computed tomography changes predict major hemorrhage after streptokinase in acute ischemic stroke. *Stroke* 2002;**33**:2236–42.
61. **Levy DE,** Brott TG, Haley EC Jr, *et al*. Factors related to intracranial hematoma formation in patients receiving tissue-type plasminogen activator for acute ischemic stroke. *Stroke* 1994;**25**:291–7.
62. **Ciccone A,** Motto C, Aritzu E, *et al*. Negative interaction of aspirin and streptokinase in acute ischemic stroke: further analysis of the Multicenter Acute Stroke Trial-Italy. *Cerebrovasc Dis* 2000;**10**:61–4.
63. **Derex L,** Hermier M, Adleleine P, *et al*. Clinical and imaging predictors of intracerebral hemorrhage in stroke patients treated with intravenous tissue plasminogen activator. *J Neurol Neurosurg Psychiatry* 2005;**76**:70–5.
64. **International Stroke Trial Collaborative Group**. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet* 1997;**349**:1569–81.
65. **Ribo M,** Montaner J, Molina CA, *et al*. Admission fibrinolytic profile is associated with symptomatic hemorrhagic transformation in stroke patients treated with tissue plasminogen activator. *Stroke* 2004;**35**:2123–7.
66. **Foerch C,** Wunderlich MT, Dvorak F, *et al*. Elevated serum S100B levels indicate a higher risk of hemorrhagic transformation after thrombolytic therapy in acute stroke. *Stroke* 2007;**38**:2491–5.
67. **Dubey N,** Bakshi R, Wasay M, *et al*. Early computed tomography hypodensity predicts hemorrhage after intravenous tissue plasminogen activator in acute ischemic stroke. *J Neuroimaging* 2001;**11**:184–8.
68. **Hacke W,** Kaste M, Fieschi C, *et al*. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995;**274**:1017–25.
69. **Selim M,** Fink JN, Kumar S, *et al*. Predictors of hemorrhagic transformation after intravenous recombinant tissue plasminogen activator: prognostic value of the initial apparent diffusion coefficient and diffusion-weighted lesion volume. *Stroke* 2002;**33**:2047–52.
70. **Alsop DC,** Makovetskaya E, Kumar S, *et al*. Markedly reduced apparent blood volume on bolus contrast magnetic resonance imaging as a predictor of hemorrhage after thrombolytic therapy for acute ischemic stroke. *Stroke* 2005;**36**:746–50.
71. **Warach S,** Latour LL. Evidence of reperfusion injury, exacerbated by thrombolytic therapy, in human focal brain ischemia using a novel imaging marker of early blood-brain barrier disruption. *Stroke* 2004;**35**(11 Suppl 1):2659–61.
72. **Kim EY,** Na DG, Kim SS, *et al*. Prediction of hemorrhagic transformation in acute ischemic stroke: role of diffusion-weighted imaging and early parenchymal enhancement. *Am J Neuroradiol* 2005;**26**:1050–5.
73. **Kakuda W,** Thijs VN, Lansberg MG, *et al*. DEFUSE Investigators. Clinical importance of microbleeds in patients receiving IV thrombolysis. *Neurology* 2005;**65**:1175–8.
74. **Derex L,** Nighoghossian N, Hermier M, *et al*. Thrombolysis for ischemic stroke in patients with old microbleeds on pretreatment MRI. *Cerebrovasc Dis* 2004;**17**:238–41.
75. **Fiehler J,** Albers GW, Boulanger JM, *et al*, the MR STROKE Group. Bleeding risk analysis in stroke imaging before thromboLysis (BRASIL): pooled analysis of T2*-weighted magnetic resonance imaging data from 570 patients. *Stroke* 2007;**38**:2738–44.
76. **Derex L,** Nighoghossian N. Intracerebral haemorrhage after thrombolysis for acute ischemic stroke. An update. *J Neurol Neurosurg Psychiatry* 2008;Jan 25 [epub ahead of print].
77. **Fiehler J,** Remmele C, Kucinski T, *et al*. Reperfusion after severe local perfusion deficit precedes haemorrhagic transformation: an MRI study in acute stroke patients. *Cerebrovasc Dis* 2005;**19**:117–24.
78. **Kim D,** Ford GA, Kidwell CS, *et al*, UCLA Intra-Arterial Thrombolysis Investigators. Intra-arterial thrombolysis for acute stroke in patients 80 and older: a comparison of results in patients younger than 80 years. *AJNR Am J Neuroradiol* 2007;**28**:159–63.

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B R Thanvi, S Treadwell and T Robinson

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Notes