

Review Article

Post Thrombolysis Intracerebral Haemorrhage: A Review of the Current Understanding of Risk Factors and Prediction Models

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Submitted: 12 December 2015**Accepted:** 03 March 2016**Published:** 04 March 2016**Copyright**

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OPEN ACCESS**Keywords**

• Thrombolysis; IV tPA; Risk factors; Ischemic stroke; Intracerebral haemorrhage; Treatment; Plasminogen activator; Stroke severity; Diabetes and hyperglycaemia; Hypertension; Anti-thrombotic; Antiplatelet; Time; Renal impairments; CT; MRI; Risk score models; Cucchiara; SEDAN; HAT; GRASP; SITS-SICH

Abstract

Since 1996, Intravenous thrombolysis by recombinant tissue plasminogen activator has been increasingly utilized for the treatment of acute ischemic stroke. However, a small proportion of patients develop post thrombolysis intracerebral haemorrhage which negates the beneficial effects of thrombolysis. The incidence of symptomatic intracerebral haemorrhage ranged from 2.2 to 11% and leads to increased mortality up to 47%. Stroke severity and hyperglycaemia are reasonably robust risk factors for post thrombolysis intracerebral haemorrhage. However, with the emergence of advanced neuroimaging techniques, novel imaging markers for intracerebral haemorrhage have been identified. It is the aim of this review article to examine the current understanding of risk factors and risk assessment scores of intracerebral haemorrhage post thrombolysis.

ABBREVIATION

AHA/ASA: American Heart Association And American Stroke Association; AIS: Acute Ischaemic Stroke; ASPECTS: The Alberta Stroke Programme Early CT Score; ATLANTIS: Alteplase Thrombolysis For Acute Noninterventional Therapy In Ischemic Stroke; DEFUSE: The Diffusion And Perfusion Imaging Evaluation For Understanding Stroke Evolution; ECASS: European Cooperative Acute Stroke Study; EPITHET: The Echoplanar Imaging Thrombolytic Evaluation Trial; ESCAPE: Endovascular Treatment For Small Core And Anterior Circulation Proximal Occlusion With Emphasis On Minimizing CT To Recanalization Times; EXTENDED - IA: The Extending The Time For Thrombolysis In Emergency Neurological Deficits-Intra-Arterial; FLAIR: Imaging And Fluid-Attenuated Inversion Recovery; GFR: Glomerular Filtration Rate; GRASPS: The Glucose Race Age Sex Pressure Stroke Severity Score; HAT Score: The Haemorrhage After Thrombolysis Score; ICH: Intracerebral Haemorrhage; ICP: Intracranial Pressure; IST3: The Third International Stroke Trial; IV Tpa: Intravenous Tissue Plasminogen Activator; IV Tpa: Intravenous Tissue Plasminogen Activator; MR CLEAN: Multicentre Randomized Clinical Trial Of Endovascular Treatment For Acute Ischemic Stroke In The Netherlands; NINDS: National Institute Of Neurological Disorders And Stroke; PROACT: Prolyse In Acute Cerebral Thromboembolism Trial; REVASCAT: Endovascular Revascularization With Solitaire Device Versus

Best Medical Therapy In Anterior Circulation Stroke Within 8 Hours; SAINT: Stroke-Acute Ischemic NXY Treatment; SEDAN: Sugar (S) Early Infarct Signs (E) Dense Cerebral Artery Sign On Admission Computed Tomography Scan (D) Age (A) And NIH Stroke Scale On Admission (N); SICH: Symptomatic Intracerebral Haemorrhage; SITS-ISTR: Safe Implementation Of Treatment In Stroke - International Stroke Thrombolysis Register; SITS-MOST: Safe Implementation Of Thrombolysis In Stroke-Monitoring Study; SITS-SICH: Safe Implementation Of Thrombolysis In Stroke Risk Score; SWIFT-PRIME: Solitaire With The Intention For Thrombectomy As Primary Endovascular Treatment; TXA: Tranexamic Acid

INTRODUCTION

Intravenous recombinant tissue plasminogen activator (IV tPA) is the recommended treatment for acute ischaemic stroke, supported by guidelines of American Heart Association and American Stroke Association (AHA/ASA) and the American College of Chest Physicians [1,2]. Approved by the US Food and Drug Administration (FDA) in 1996 for treatment of acute ischaemic stroke (AIS), IV tPA (or alteplase) is the only thrombolytic agent approved for this indication to date [3]. Based on the results of the outcome of the European Cooperative Acute Stroke Study (ECASS) III study, the American Stroke Association has counselled the extension for IV tPA treatment window to 4.5 hours in carefully selected patients [4].

Besides IV tPA, endovascular mechanical thrombectomy, may be employed in a proportion of acute ischaemic stroke with large artery occlusion, either as a standalone therapy or bridging therapy with IV tPA. Mechanical thrombectomy has several potential advantages, including a longer time window and higher reperfusion rates (up to 82%) [5]. The recent 5 randomized controlled studies, including MR CLEAN, EXTENDED-IA, ESCAPE, SWIFT- PRIME, REVASCAT provided evidence of superiority of mechanical thrombectomy over IV tPA alone in patients with large artery occlusion [6-10].

However, IV tPA remains relevant as mechanical thrombectomy is not widely available in some countries due to the lack of access to neurointerventionists and equipment (neurovascular angiography suites). Data collected using the Nationwide Inpatient Sample database in the U.S. for 2008 showed that only 9.5% (296/ 3121) of hospitals in urban settings offered mechanical revascularization, whereas no rural hospitals performed the procedure (0/2161) [11]. Furthermore, IV tPA remains useful in acute ischaemic stroke without large artery occlusion.

However, up to 6.8 % patients developed intracerebral haemorrhage after having received IV tPA [12]. Symptomatic intracerebral haemorrhage (sICH) is defined as any intracerebral haemorrhage identified by neuroimaging in association with clinical deterioration during the first 36 hours post thrombolysis [13]. The aim of this review article is to examine the current understanding of risk factors of sICH post thrombolysis and their relevance in clinical practice. Risk factors include age, gender and weight, stroke severity, diabetes and hyperglycaemia, blood pressure, previous treatment with antiplatelet and antithrombotic, time to thrombolysis, renal impairment, platelet count and cardiac dysfunction. Furthermore, our understanding of risk factors for post IV tPA sICH have improved due to the advent of modern radiological techniques, such as CT angiogram and MRI. We also outline several clinical risk assessment systems for the prediction of post IV tPA ICH, including HAT, GRASPS, Cucchiara, SITC-SICH and SEDAN [14-18].

The prevalence and consequences of symptomatic intracerebral haemorrhage

National Institute of Neurological Disorders and Stroke (NINDS) trial performed in 1995 defined symptomatic intracerebral haemorrhage (sICH) as haemorrhage CT within 36 hours of treatment, together with clinical deterioration [19]. In this study, the rate of sICH at 36 hrs in the group treated with IV tPA within 3hrs after onset was 6.4% compared to 0.6 % in the placebo group. Both ECASS I and ECASS II defined sICH as a combination of intracerebral haemorrhage with more than 4 points increased on the National Institutes of Heart Stroke Scale (NIHSS) [5]. The incidence of sICH ranged from 2.2% to 11% in groups treated with IV tPA [20-24]. Of note, ICH was associated with high mortality up to 47% [19,25]. A summary of sICH in randomised clinical trials of IV tPA in acute ischemic stroke is shown in table 1.

Treatment available for sICH

If patient is suspected to have developed ICH, IV tPA infusion

must be halted. After diagnosis is confirmed by neuroimaging, transfusion with cryoprecipitate containing factor VIII and platelets (6-8 units) should be commenced [29]. Recombinant factor VIIa and fresh frozen plasma are also considered options to counter the effect of IV tPA [30]. However, these agents are limited by cost and difficulty in preparation and may incur moderate risk of hypersensitivity transfusion reaction [30]. Therefore, haemostatic medications, such as Tranexamic acid (TXA) which prevent the activation of plasminogen to plasmin, are reasonable alternatives to reverse the effects of IV tPA [30]. In addition, there is no evidence supporting blood pressure control and surgical management for post thrombolysis ICH [29,31]. Surgical intervention may be required but is discouraged if the fibrinolytic effects of IV tPA persists [29,31]. Monitoring of patients in a neurointensive care unit with intracranial pressure (ICP) is highly recommended.

Risk factors for post IV tPA sICH

1) Stroke Severity: Higher National Institutes of Health Stroke Scale scores (NIHSS) is associated with greater risk of post thrombolysis sICH [31]. Mone et al showed that in a study of 10242 patients, NIHSS score higher than 20 is 10 times more likely to develop ICH post thrombolysis [31]. Furthermore, Cucchiara et al analysed patients enrolled in Stroke-Acute Ischemic NXY Treatment (SAINT) I and SAINT II Trials and highlighted the link between higher NIHSS and increase in risk of developing sICH post IV tPA (OR, 1.07 per one point of NIHSS increase, 1.04 to 1.11, $P < 0.001$) [32]

2) Diabetes mellitus and Hyperglycaemia: Numerous studies have shown an independent association of baseline hyperglycaemia or history of diabetes mellitus and risk of sICH [18,33,34]. Poppe et al showed that the rate of sICH among hyperglycaemic patients (Baseline glucose > 8.0 mmol/l) was 6.8% compared to 3.6% in norm glycaemic patients [35]. Moreover, according to Prolyse in Acute Cerebral Thromboembolism Trial (PROACT) II trial, intracerebral haemorrhage developed in 36% of patients with baseline serum glucose > 200 mg/dL [12]. Additionally, in a multivariable analysis of both treatment and placebo arms of the NINDS IV tPA Stroke Trial, the risk of sICH increased (OR 1.75, 95% CI 1.11–2.78) for every 100mg/dl increase in admission glucose.

3) Blood Pressure: Hypertension is a risk factor for developing post IV tPA sICH [36-38]. In Tsvigoulis' study of 510 patients with ischemic stroke treated with intravenous tissue plasminogen activator, 6.1% patients developed sICH. Tsvigoulis showed that pre-treatment high blood pressure (systolic blood pressure > 185 or diastolic blood pressure > 110 mm Hg prior to IV tPA bolus) were independently associated with a higher likelihood of sICH (OR, 2.59; 95% CI, 1.07 to 6.25; $P = 0.034$) [38]. This adds weight to the current guidelines of American stroke association and guideline that IV tPA should not be administered to ischaemic stroke patients when systolic blood pressure was equal or higher than 180mmHg; or diastolic blood pressure larger than 110mmHg on repeated measures prior to study [36]. The majority of clinical studies developed strict blood pressure parameters before and after the administration of IV tPA.

4) Previous treatment with anti-thrombotic and

Table 1: Randomized clinical trials of intravenous IV tPA in acute ischemic stroke.

Analysis	Age	IV tPA dose	Treatment window	incidence of ICH in IV tPA vs placebo	Mortality of IV tPA vs placebo	Mortality in patients with post IV tPA ICH
NINDS 1995	No age limit 49 patients over the age of 75.	IV tPA 0.9 mg/kg	3 hours (1.5)	IV tPA 6.4% sICH versus placebo 0.6%; P= 0.001	In 90 days IV tPA 17% versus placebo 21%; P=0.30	47%
ECASS I 1995 [26]	18-80 years old	IV tPA 1.1 mg/kg	6 hours (4.3)	IV tPA 20% versus placebo 7%; P=0.001	in 30-day mortality IV tPA 18% versus placebo 13%; P=0.08	N/A
ECASS II 1998 [27]	18-80 years old	IV tPA 0.9 mg/kg	6 hours (NR 80% between 3 and 6 hours)	IV tPA 8.8% sICH versus placebo 3.4%	IV tPA 43 patients versus placebo 42	N/A
ECASS III 2009 [4]	18-80 years old	IV tPA 0.9 mg/kg	3-4.5 hours	IV tPA 2.4% sICH versus placebo 0.2%; P=0.008	IV tPA 7.7% versus placebo 8.4%; P=0.68	N/A
ATLANTIS A 2000 [38]	18-80 years old	IV tPA 0.9 mg/kg	6 hours (4.6)	IV tPA 11% sICH versus placebo 0%; P= 0.01	in 90 days IV tPA 23% versus placebo 7%; P=0.01	N/A
ATLANTIS B 1999 [25]	18-80 years old	IV tPA 0.9 mg/kg	3–5 hours (4.6)	IV tPA 7% sICH versus placebo 1.1%; P= 0.001	IV tPA 11% versus placebo 6.9%; P=0.09	Fatal ICH (0.3% vs 3.0% [P<.001]). (Y)
SITS-ISTR 2008 [23]	>18 years old	IV tPA 0.9 mg/kg	3-4.5 hours Compare IV tPA treatment within 3 hours and IV tPA treatment within 3-4.5 hours	IV tPA within 3 hrs 2.2% sICH versus IV tPA within 3-4.5 hrs 1.6 % sICH; P=0.24)	No difference in mortality after 6 months 12.7% (70 of 551) versus 12.2% (1263 of 10 368)	N/A
SITS- MOST 2006 [21]	18-80 years old	IV tPA 0.9 mg/kg	3 hours	1.7% sICH (107/6444; 95% CI 1.4-2.0)	Overall mortality at 3 months 11.3% (701/6218; 10.5-12.1)	N/A
IST 3 2012 [22]	>18 years old 1617 (53%) > 80 years of age	IV tPA 0.9 mg/kg	3-4.5 hours	IV tPA 7% sICH versus 1% placebo. OR 6-94, 95% CI 4-07-11-8; absolute excess 58/1000, 95% CI 44-72	Overall mortality within 6 months (IV tPA 27% = 27% in placebo)	N/A
EPITHET 2012 [28]	>18 years old	Not found	3-6 hours	The primary outcome measure of geometric mean infarct growth was significantly attenuated by a ratio of 0.58 with alteplase compared to placebo (1.02 vs 1.77; 95% CI, 0.33–0.99; P=0.0459).	N/A	N/A

Abbreviation: ATLANTIS: Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ECASS: European Cooperative Acute Stroke Study; EPITHET: The Echoplanar Imaging Thrombolytic Evaluation Trial; IST3: the third international stroke trial; IV tPA: intravenous tissue plasminogen activator; NINDS: National Institute of Neurological Disorders and Stroke; sICH: Symptomatic intracerebral haemorrhage; SITS-ISTR: safe implementation of treatment in stroke - International Stroke Thrombolysis Register; SITS-MOST: Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study

antiplatelet: Previous treatment with Warfarin or antiplatelet medications showed an association with post thrombolysis haemorrhage [39,40]. Furthermore, Prabhakaran et al showed that the rate of sICH was nearly 10-fold higher among patients on warfarin [39]. In addition, Uyttenboogaart et al reported the results of 301 consecutive patients who received intravenous IV tPA for acute ischemic stroke and demonstrated significant

increase in the incidence of ICH in patients who had previous exposure to antiplatelet (13.5% vs 2.8%, P = 0.003) [41].

5) Risk of Symptomatic ICH and Outcomes Related to Time: Delaying treatment with IV tPA increases the risk of sICH. Clark et al found that delay treatment with IV tPA significantly raises the rate of sICH within 10 days (11% versus 0%, P<0.01) and mortality at 90 days (23% versus 7%, P<0.01). This is

Table 2: Risk assessment scores used to predict ICH post IV tPA.

Score system	Risk factors included	Score/ Corresponding risk of ICH		Prognostic discriminatory ability (C statistic)
Cucchiara et al [16]	60 years old = 1 point; - baseline NIHSS > 10 = 1 point; - Platelet count < 150,000/mm³ = 1 point. - Blood Glucose > 8.325 mmol/L = 1 point;	0 1 2 ≥3	2.6% 9.7% 15.1% 37.9%	0.69
SEDAN [18]	- baseline blood glucose (8.1–12.0mmol/l) = 1 point >12.0mmol/l = 2 points - Early infarct sign = 1 point - Hyper dense cerebral artery sign = 1 point >75 years old = 1 point - NIHSS ≥10 = 1 point	0 1 2 3 4 5 6	1.4 % 2.9 % 8.5 % 12.2 % 21.7 % 33.3 % > 33.3%	N/A
HAT [14]	- Baseline blood glucose > 200 mg/dl upon admission = 1 point - NIHSS score from 15-20 =1 point - NIHSS score ≥20 = 2 points - Hypo density on initial head CT scan. < 1/3 of MCA territory =1 point ≥ 1/3 of MCA territory = 2 points	0 1 2 3 >3	2% 5% 10% 15% 44%	0.72 (ICH) 0.74 (sICH) 0.79 (ICH with fatal outcome)
GRASPS [15]	- Age: ≤60 8 61-70 11 71-80 15 - NIHSS: 0-5 25 6-10 27 11-15 34 16-20 40 >20 42 - Systolic blood pressure (mmHg) <120 10 120-149 14 150-179 18 ≥180 21 - Blood glucose (mmol/L) <100 2 100-149 6 ≥150 8 - Race: - Asian 9 - Non-Asian 0 - Gender: - Male 4 - Female 0	45 -57 58-63 64-68 69-71 72-73 74-76 77 78-79 80-81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100	1% 2% 3% 4% 5% 6% 7% 8% 9% 10% 11% 12% 13% 14% 15% 16% 17% 18% 19% 20% 22% 23% 25% 26% 28% 30% 31% 33%	0.68
SITR-SICH [17]	- Aspirin+clopidogrel = 3 points - Aspirin monotherapy = 2 points - NIHSS ≥13 = 2 points - NIHSS 7–12= 1 point - Baseline Glucose ≥180 mg/dL = 2 points - Age ≥72 y =1 point - Systolic BP ≥146 mm Hg = 1 point - Weight ≥95 kg = 1 point - Onset-to-treatment time ≥180 min = 1 point - History of hypertension = 1 point	0–2 3–5 6–8 ≥9	0.2%–0.6% 1.3%–1.7% 3.1%–4.1% 5.9%–12.5%	0.70

Abbreviation: GRASPS: the Glucose Race Age Sex Pressure Stroke Severity score; HAT score: the Haemorrhage After Thrombolysis score; ICH: intracerebral haemorrhage; IV tPA: intravenous tissue plasminogen activator; SEDAN: Sugar (S) Early infarct signs (E) dense cerebral artery sign on admission computed tomography scan (D) age (A) and NIH Stroke Scale on admission (N); SITR-SICH: the Safe Implementation of Thrombolysis in Stroke risk score

because 85% of patients in his study was treated with IV tPA 3 hours after onset [25]. sICH was more prevalent among patients treated within 5 and 6 hours after the onset of stroke. In study investigating the outcomes in patients treated with IV tPA within 0-6 hours after stroke onset, Clark et al showed that patients treated within 5-6 hours had higher rate of post IV tPA sICH (18.2%) than the overall rate of post tPA sICH in the study (11%) [42].

6) Renal impairment: Renal impairment is a possible risk factor for sICH post IV tPA [21]. Mash et al studied 224 patients treated with IV tPA within 4.5 hours after the onset of stroke. Patients' renal function was assessed by estimating the glomerular filtration rate (eGFR) from serum creatinine level. Neuroimaging was obtained 1 day post IV tPA and for any change in neurologic status to evaluate for ICH. Serum creatinine > 1.0 mg/l indicated impairment of renal function. In this study, there was 5.5-fold risk of sICH when serum creatinine level was above 1.0 ng/dL [40]. In addition, only 1.8% of patients with normal renal function had post IV tPA sICH ($p = 0.010$) while 10.6% of patients with elevated serum creatinine level had post IV tPA sICH [43].

7) Radiological factors:

CT: Signs of early ischaemic changes shown on plain CT, such as hypo density, reduction in grey-white differentiation, swelling with sulcal effacement, cerebral oedema, acute ischemia, vessel thrombosis and background white matter disease can predict the likelihood of developing post IV tPA sICH [44,45]. The Alberta Stroke Programme Early CT Score (ASPECTS) is a quantitated CT score that can help predict functional outcome and risk of intracerebral haemorrhage post thrombolytic therapy for acute ischemic stroke [45]. ASPECTS score of 7 or less is a predictive factor for more frequent sICH. Moreover, when comparing to patients without leukoaraiosis on CT of the brain, leukoaraiosis is also associated with symptomatic haemorrhagic transformation (OR 1.9, 95%-CI 0.78-4.68, $P = 0.16$) and worse clinical outcomes after IV tPA treatment [45]. However, it is very difficult to discriminate many such features such as, hypo attenuation of middle cerebral artery territory, by CT in the hyperacute period. This confusion can lead to inaccurate quantification, and significant inter-rater variability [46]. Machine learning techniques can be used to better recognise these subtle features [47] and hence may improve our ability to predict post IV tPA sICH.

MRI: The Diffusion and perfusion imaging Evaluation For Understanding Stroke Evolution (DEFUSE) study defined MRI reperfusion as a decrease of at least 10ml or 30% of PWI lesion volume between the baseline and follow-up MRI [48]. In DEFUSE study, when considering the baseline variables, reperfusion status, and the link between baseline variables and reperfusion status, a single independent risk factor of any sICH is the interaction between baseline DWI lesion volume and reperfusion status (odds ratio 1.77; 95% CI 1.25 to 2.50 per 10 mL change in DWI lesion volume) and major sICH (odds ratio 1.90; 95% CI 1.21 to 3.00 per 10 mL change in DWI lesion volume) [49]. DWI lesion site is also reported to be a risk factor for sICH in a study done on 645 patients (OR 1.080; 95%CI 1.012-1.153 per 10 ml increase) [50]. For small (≤ 10 ml), moderate (10-100 ml)

and large (>100 ml) DWI lesions, proportion of sICH is 2.8, 7.8 and 16.1% respectively ($p < 0.05$) [50]. Therefore, for ischaemic stroke patients who were treated with IV tPA between 3 and 6 hours after the onset of stroke, large DWI lesion volumes and early reperfusion on MRI are significant risk factors for developing sICH.

T2* weighted MRI imaging and fluid-attenuated inversion recovery (FLAIR) sequences may estimate the risk of developing sICH post IV tPA. Cho et al showed that FLAIR hyper intensity is associated with sICH-2 (OR, 10.44; 95% CI, 1.11 to 98.35) [51].

Risk score models

Various risk score models which aim at better identification of patients at high risk of sICH in thrombolysis have been developed. They include the Haemorrhage After Thrombolysis (HAT) score, the Glucose Race Age Sex Pressure Stroke Severity (GRASPS) score, Cucchiara et al, the Safe Implementation of Thrombolysis in Stroke (SITS)-sICH risk score, the NIHSS (SEDAN) score [14-18]. The risk score systems listed above use clinical risk factors, such as age, gender, NIHSS, glucose, blood pressure and platelet count. Radiological factors are also included in HAT and SEDAN score. These were converted to a scoring system that corresponds to the likelihood of developing ICH post IV tPA. After examining the effectiveness of these risk score in a Taiwanese population, Sung et al concluded that Cucchiara score, the HAT score, and the SITS-sICH risk score predicted sICH reasonably well regardless of which sICH definition was used [52]. The GRASPS score only predicted well in 1 or 2 definition of sICH. However, only discriminatory ability of the HAT score is at acceptable level [52]. Therefore, we can improve the effectiveness of these risk score systems by investing in more research into both clinical factors and radiological factors.

Table 2 is a summary of the risk models (Cucchiara, SEDAN, HAT, GRASPS, SITS-sICH).

CONCLUSION

The risk of sICH after treatment with IV tPA is documented in clinical trials. Clinical risk factors (e.g. age and hyperglycaemia) for sICH have been extensively investigated. However, with the advent of neuroimaging techniques, novel imaging markers for the development of sICH have been identified. Several risk assessment scores have incorporated these risk factors, improving the accuracy of prediction of sICH post IV tPA.

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Cite this article

Nguyen Vu CL, Yan B (2016) Post Thrombolysis Intracerebral Haemorrhage: A Review of the Current Understanding of Risk Factors and Prediction Models. *J Neurol Disord Stroke* 4(1): 1107.