

# The Risk of Symptomatic Intracranial Hemorrhage after Thrombolysis for Acute Stroke: Current Concepts and Perspectives

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## Abstract

**Background:** Thrombolysis is the standard of treatment for acute ischemic stroke, with a time window of up to 4½ h from stroke onset. Despite the long experience with the use of recombinant tissue plasminogen activator and the adherence to protocols symptomatic intracranial hemorrhage (SICH) may occur in around 6% of cases, with high-mortality rate and poor-functional outcomes. Many patients are excluded from thrombolysis on the basis of an evaluation of known risk factors, but there are other less known factors involved. **Objective:** The purpose of this work is to analyze the less known risk factors for SICH after thrombolysis. A search of articles related with this field has been undertaken in PubMed with the keywords (brain hemorrhage, thrombolysis, and acute ischemic stroke). Some risk factors for SICH have emerged such as previous microbleeds on brain magnetic resonance imaging, leukoaraiosis, and previous antiplatelet drug use or statin use. Serum matrix metalloproteinases have emerged as a promising biomarker for better selection of patients, but further research is needed. **Conclusions:** In addition to the already known risk factors considered in the standard protocols, an individualized evaluation of risks is needed to minimize the risk of brain hemorrhage after thrombolysis for ischemic stroke.

**Keywords:** Acute stroke, brain hemorrhage, thrombolysis complications

## INTRODUCTION

Thrombolysis is the first line of treatment in hyperacute ischemic stroke, and eventually followed by mechanical thrombectomy. Recombinant tissue plasminogen activator (rt-PA) is the only agent approved by the European Medicines Evaluation Agency (EMA) since 2002 for acute ischemic stroke within 3 h of stroke onset according to the benefits observed in multicenter clinical trials in North America and Europe.<sup>[1-3]</sup> A registry and a protocol was created to monitor the outcomes and safety (ISTR, SITS-MOST/www.acutestroke.org/SM\_Protocol/SITS-MOST\_final\_protocol.pdf). The time window was extended to 4.5 h on light of the benefits observed in the European Cooperative Acute Stroke Study III (ECASS [III]) trial,<sup>[4]</sup> with a new registry called Safe implementation of thrombolysis in upper time window monitoring study (SITS-UTMOST).<sup>[5]</sup>

The major complication of thrombolysis is symptomatic brain hemorrhage in the area of infarction symptomatic intracranial hemorrhage (SICH), which happens in around 6.4% of cases in the NINDS trial,<sup>[1,2]</sup> or higher in the ECASS II trial (8.8%), but SICH can also appear in remote or extracerebral brain regions as well in 1.3%–2% of cases.<sup>[2,3]</sup> The in-hospital mortality due to SICH after thrombolysis was 52.3% (67/128 cases), independently of treatment.<sup>[6]</sup> Furthermore, SICH appeared after thrombolysis for pulmonary embolism in two studies, in 1.8% (176/9705) and in 1.9% (6/302) of treated patients, respectively, and with poor outcomes.<sup>[7,8]</sup> The frequency of BH was low after

thrombolysis for AMI, 9 cases out of 1700 patients treated with rt-PA (0.53%).<sup>[9]</sup>

Most postthrombolysis hematomas occur in the area of infarction [Figure 1a and b] because of damaged brain tissue, loss of hemostatic control, and later reperfusion, whereas remote hemorrhages tend to occur in preexisting brain pathologies and/or coagulopathies.<sup>[10]</sup> Amyloid angiopathy has been associated with remote brain hemorrhages.<sup>[11,12]</sup>

Given the high mortality and poor functional outcome of BH after thrombolysis, many studies have been focused on the predictive factors. Some risk factors are well known, and they are taken into account in the standard protocols by preventing clinicians to administer rt-PA in patients with these factors (noncontrolled hypertension, high elevation of plasma glucose, low platelet count, previous surgery within the 3 months, NIHSS score higher than 25 points, early signs

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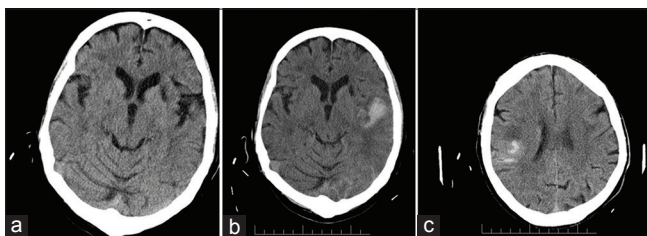
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of infarction on brain CT, duration of stroke symptoms longer than 4.5 h, symptoms with unknown onset time, and so on).<sup>[13]</sup> Despite discarding patients with these factors for thrombolysis SICH can occur.

I have searched articles in PubMed, related with the field of SICH after thrombolysis in patients with acute ischemic stroke. The key words used were: thrombolysis, brain hemorrhage, and acute ischemic stroke. From the initial 695 articles, only 51 were considered informative enough with regard to risk factors for SICH after thrombolysis for acute ischemic stroke.

There is a consensus in several factors such as higher NIHSS score, age, systolic blood pressure, previous antiplatelet treatment, and high glucose levels in the serum in two great registries.<sup>[14,15]</sup> The Italian registry including 15,949 patients developed a prediction model based on 10 variables that were predictors of BH.<sup>[14]</sup> The European one with 31,627 patients found 9 predictive variables.<sup>[15]</sup> However, the protocols are not sacrosanct; alteplase can be administered even in acute stroke with unknown onset time in cases with positive MRI-diffusion-weighted imaging and negative FLAIR imaging.<sup>[16]</sup>

Preexisting cerebral microbleeds have been considered a risk factor for BH after thrombolysis, and it was confirmed in three meta-analyses from pooled data of medical literature with 2702,<sup>[17]</sup> 1704,<sup>[18]</sup> and 2479<sup>[19]</sup> patients. According to three meta-analyses from 15/11/11 trials with a similar number of treated patients (6967/6912/7194), the presence of leukoaraiosis was associated with an increased risk of SICH and poor outcomes.<sup>[20-22]</sup> Both microbleeds and leukoaraiosis were associated with remote location SICH.<sup>[23,24]</sup> Extensive leukoaraiosis also increased the risk of remote SICH and poor outcomes in a cohort of 503 patients<sup>[25]</sup> and in another cohort of 2485 Finnish patients.<sup>[26]</sup> However, the data of 614 patients from a prospective registry did not show such an association, but leukoaraiosis predicted poor functional outcomes after stroke.<sup>[27]</sup> Cardioembolic stroke is an independent risk factor for SICH in two far-East countries.<sup>[28,29]</sup>



**Figure 1:** (a) Brain computed tomography before thrombolysis. Old infarction in the left basal ganglia. The patient fulfilled the criteria of SITS-MOST for intravenous recombinant tissue plasminogen activator. (b) Brain computed tomography, carried out 24 h after thrombolysis with hemorrhage type 2 in the area of infarction in the left posterior MCA (middle cerebral artery), with clinical worsening. (c) Brain computed tomography after thrombolysis small hemorrhagic transformation (HI-2) without clinical worsening

From a prospective stroke database, the only predictor of SICH was the change in the level of consciousness, which happened in 108 out of 511 patients and 19 of them had SICH (odds ratio [OR]: 6.62; 1.64–26.7).<sup>[30]</sup>

The question on whether antiplatelet treatment for prevention of ischemic stroke prior ischemic stroke treated with thrombolysis increases or not the risk of SICH has not been completely elucidated. In two systematic review and meta-analysis, the conclusions were discordant; in the first one with 7 clinical trials and 4376 patients, there was no association between previous antiplatelet treatment and SICH, nor was the functional outcome worse.<sup>[31]</sup> In the second one with 108,588 patients from 19 studies, there was a positive association between the use of antiplatelet drugs and SICH, but the differences regarding outcomes and mortality were not significant.<sup>[32]</sup> In the last American heart society/American stroke association (AHS/ASA) guidelines of 2018 for the early management of acute ischemic stroke, the prior use of antiplatelet drugs does not preclude thrombolysis with t-PA, as benefits outweigh the small increased risk of SICH.<sup>[13]</sup>

With regard to previous ischemic stroke within 3 months before receiving thrombolysis, it was not associated with increased risk of SICH but with increased risk of death, according to the data of a multicenter registry in the USS comprising 36,599 patients treated with thrombolysis.<sup>[33]</sup> From an European Registry with 13,007 patients included, neither was seen an increased risk of SICH, with no worse outcomes.<sup>[34]</sup> Prior asymptomatic SICH in the context of ischemic stroke did not increase the risk of SICH after thrombolysis in a retrospective cohort of 640 patients.<sup>[35]</sup>

Prior statin use has been associated to increased risk of SICH, but it did not have any impact on outcomes according to cases series of 311 and 182 patients treated<sup>[36,37]</sup> and three European registries totaling 2482 patients.<sup>[37-39]</sup> In another registry of 606 patients, the risk of SICH was not increased (OR: 0.57; 95% confidence interval [CI]: 0.22–1.49)<sup>[40]</sup> and in a meta-analysis of 11 studies and 6438 patients, the statin use neither increased the risk of SICH nor was associated with more favorable outcomes.<sup>[40]</sup>

Some MRI-based technique such as diffusion (apparent diffusion coefficient [ADC]),<sup>[41]</sup> and spin-label MRI after reperfusion (arterial spin labelling [ASL]),<sup>[42]</sup> may offer some aid in the prediction of SICH postthrombolysis. An ADC ratio (ADC in the affected area/ADC in the normal contralateral area) <0.65 was an independent predictor of hemorrhagic transformation, so was FLAIR hyperintensity.<sup>[41]</sup> Focal hyperperfusion in the damaged area after reperfusion on ASL in a ratio higher than 1.5 (ipsilateral/contralateral) was also a reliable predictor of hemorrhagic transformation.<sup>[42]</sup>

The use of the ASPECTS CT-based scale prior thrombolysis is common worldwide to stratify the risk of bleeding after thrombolysis. According to data from the ECASS II trial,

the patients with scores  $\leq 7$  points were at increased risk of parenchymal brain hemorrhage (Relative risk [RR]: 18.9; 95% CI: 1.6–138) as those with scores of 8–10.<sup>[43]</sup>

Patients who underwent mechanical thrombectomy in hyperacute stroke were not at increased risk of brain hemorrhage as those who did not, according to a systematic review comprising 1287 patients.<sup>[44]</sup> The off-label use of rt-PA (e.g., age older than 80, previous stroke and diabetes, previous surgery within 3 months prior of stroke onset, prior oral anticoagulation, systemic diseases, intracranial tumors, seizures at onset, and NIHSS score higher than 25 points) did not result in higher rates of SICH or poorer functional outcome than in the on-label group in a retrospective study of 505 patients.<sup>[45]</sup>

**Table 1: Classification of brain hemorrhages postthrombolysis for acute ischemic stroke, according to the European Cooperative Acute Stroke Study II trial<sup>[3]</sup>**

ECASS classification of hemorrhagic transformation

HI

H-1: Small petechiae along margins of infarcted area

H-2: Confluent petechiae within the infarcted area; no mass effect

PH

PH-1: Hematoma less than 30% of infarcted area, with mild mass effect

PH-2: Hematoma in more than 30% of infarcted area, with notable mass effect

HI=Hemorrhagic infarction, PH=Parenchymal hemorrhage

The use of selective serotonin reuptake inhibitor (SSRI) antidepressants is associated with some trend to bleeding, but the data of an international registry with 1114 patients treated with thrombolysis and 135 treated with SSRI drugs did not show association between the use of SSRI antidepressants and the risk of SICH, mortality, or poorer functional outcome.<sup>[46]</sup>

An unresolved issue on SICH is the case definition. The criteria of ICH vary across the studies. In the NINDS trial, symptomatic ICH was defined as hemorrhage seen within 36 h of treatment and deemed to be temporally related to neurological decline.<sup>[1]</sup> The SITS-MOST criteria only considered parenchymal hemorrhages with an increase of at least 4 points in the NIHSS. The ECASS III trial defined symptomatic ICH as evidence of hemorrhage on CT or MRI that was felt to be associated with an increase in NIHSS score of  $\geq 4$ , and SICH occurred in 2.4% of patients in the extended window of 3–4.5 h.<sup>[4]</sup> The ECASS II criteria distinguish hemorrhagic infarction from parenchymal hemorrhages [Table 1].<sup>[3]</sup> In a secondary analysis of ECASS II trial, only parenchymal hematoma type 2 was associated with an increased risk for deterioration at 24 h after stroke onset.<sup>[47]</sup> Of course, small hemorrhagic transformations do not have clinical implications [Figure 1c]. The variability of criteria used may contribute to the differences found in the different studies and meta-analysis. Thus, the incidence of SICH tends to be higher in clinical trials than in the registries (7.4% vs. 3.5%).<sup>[48]</sup>

**Table 2: Factors predictive of symptomatic intracranial hemorrhage and that do not exclude intravenous thrombolysis. Results from meta-analysis and large registries**

Predictor	Number of trials and patients	Risk of SICH OR/RR and 95% CI	Unfavourable outcome (death or dependence)
<b>Author</b>			
Prior statin use	11 studies with 6438 patients	1.55 (1.23-1.95)	0.99 (0.88-1.12) NS
Meseguer 2012			
Leuko-araiosis	11 trials, 6912 patients	1.89 (1.51-2.37)	Not given
Lin, 2106			
Leuko-araiosis,	11 studies, 7194 patients	1.55 (1.17-2.06)	1.61 (1.44-1.79)
Charidimou 2016			
Leuko-araiosis	15 studies, 6967 patients	1.65 (1.26-2.16)	1.30 (1.19-1.42)
Kongbunkiat 2017			
Microbleed burden	9 studies, 2479 patients	2.36 (1.21-4.61), risk proportional to the burden	Not given
Tsivgoulis 2016			
Microbleed burden	8 studies, 1704 patients	2.87 (1.73-4.79)	Not given
Charidimou 2015			
Microbleed burden	11 studies, 2702 patients	2.14 (1.34-3.42)	1.58 (1.08-2.31)
Wang S, 2017			
Recent ischemic stroke	Several registries with 36,599 patients	0.9 (0.6-1.4) NS	1.5 (1.2-1.9)
Merkler			
Antiplatelet drug use	19 studies with 108,588 patients	1.70 (1.47-1.97)	1.46 (1.22-1.75)
Luo 2016			
Antiplatelet drug use	7 trials, 4376 patients	1.67 (0.75-3.72) NS	1.01 (0.55-1.86) NS
Tsivgoulis			
Antiplatelet drug	179 centers, 15,949 patients	2.23 (1.26-3.94)	Not given
Capellari 2016			

NS=Not significant, SICH=Symptomatic intracranial hemorrhage, OR=Odds ratio, CI=Confidence interval, RR=Relative risk

The search of plasmatic biomarkers for better selection of patients for thrombolysis has not yielded yet results useful enough for clinical application. The determination of serum metalloproteinases seems to be promising. A baseline level of metalloproteinase-9 7 900 ng/ml can predict SICH with 85% sensitivity and 79% specificity in accordance with the pooled values of a meta-analysis of 7 studies and 1492 patients, but heterogeneity between studies was significant, with cutoff values ranging from 140 to 900 ng/dl.<sup>[49]</sup>

Other plasmatic biomarkers have been studied for better prediction, such as F2-isoprostanes, thrombin-activated fibrinolysis inhibitor, plasminogen activation inhibitor, and the calcium-binding protein S100B. To date, there are no current recommendations for using determined plasmatic biomarkers.<sup>[50]</sup>

The main conclusions drawn by the experience with thrombolysis for acute stroke can be summarized by the secondary analysis of an individual patient data meta-analysis from the Stroke Thrombolysis Trialists (9 trials and 6756 patients), with time to treatment and stroke severity being the best predictors of global outcome. Although the sooner the better, within 4–5 h of stroke onset the benefits of thrombolysis outweigh the risks of SICH and death.<sup>[51]</sup>

In Table 2, the data of the different recent meta-analysis based on predictors of SICH after thrombolysis for acute stroke are given.

To date, we do not have treatment effective enough to reverse coagulopathy caused by thrombolysis or to prevent hematoma expansion.<sup>[52]</sup> However, the American Heart Association recommends replacing coagulation factors and platelets with the infusion of cryoprecipitate and platelets because of the alteplase-induced hypofibrinogenemia,<sup>[53]</sup> but it is only based on empirical data.

## CONCLUSIONS

Therefore, despite the better selection of patients for thrombolysis, many SICH will occur, and the decision of treatment will be for long time based on the individual balance of benefits/risks.

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## Conflicts of interest

There are no conflicts of interest.

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