Symptomatic Intracranial Hemorrhage following Intravenous Thrombolysis for Acute Ischemic Stroke: A Critical Review of Case Definitions

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Abstract

Background: Symptomatic intracranial hemorrhage (SICH) is a devastating complication of intravenous thrombolysis treatment that is associated with high mortality. Clinical trials, stroke registries and cohort studies employ different case definitions to identify stroke patients with SICH following intravenous thrombolysis. We systematically reviewed the reported rates of SICH following intravenous thrombolysis and compared their consistency with mortality outcomes. *Methods:* Studies were identified from the PubMed and Embase databases from January 1994 to July 2011 by cross-referencing the following MeSH terms: 'thrombolysis', 'recombinant tissue plasminogen activator', 'rtPA', 'hemorrhagic stroke', 'cerebral hemorrhage', 'hematoma' and 'ischemic stroke'. Demographic information, baseline National Institute of Health Stroke Scale (NIHSS) scores, time from stroke onset to intravenous thrombolysis, SICH and mortality rates were derived from published data in 7 randomized controlled trials, 7 stroke registries and 10 cohort studies (4 multicenter and 6 single center) with more than 200 consecutively recruited patients. Mortality rates were considered as the percentage of patients treated with intravenous thrombolysis who died within 90 days after stroke. *Results:* The mean age of patients included in this analysis was 68.8 years (standard deviation, SD 2.9, range 63–75), of whom 56.3% (SD 4.5, range 45–63) were men. They presented with a mean baseline NIHSS of 12.5 (SD 1.4, range 9–15) and received intravenous thrombolysis 175 min (SD 62, range 120–328) from stroke onset. The overall mean SICH and mortality rates of patients treated with intravenous thrombolysis were 5.6% (SD 2.3) and 14.7% (SD 4.8), respectively. A moderate correlation was observed between the incidence of SICH and mortality in patients treated with intravenous thrombolysis (r = 0.401, p = 0.050). The variation in SICH rates was highest across studies that reported SICH rates using the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria compared with the European Cooperative Acute Stroke Study and National Institute of Neurological Disorders and Stroke (NINDS) criteria. Studies that defined SICH as parenchymal hemorrhage with a neurological decline NIHSS ≥ 4 occurring within 36 h of intravenous thrombolysis reported a higher consistency between SICH and mortality rates (correlation coefficient 0.631). *Conclusions:* SICH rates vary considerably between studies and these differences may relate to the differences in the criteria used to define SICH. Until a case definition with high inter-rater agreement and good correlation with stroke outcomes becomes available, detailed information on the type of bleeding, the extent of NIHSS deterioration, neuroimaging features and the time from thrombolysis to diagnosis of hemorrhage should be reported to permit a correct interpretation of SICH rates.

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Introduction

Differences exist in the criteria used to define the neurological decline, cerebral hemorrhage and interval between intravenous thrombolysis and the onset of cerebral hemorrhage (online suppl. table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000339675). The initial investigators of the National Institute of Neurological Disorders and Stroke (NINDS) studies considered symptomatic hemorrhage in patients as 'contemporaneous neurological worsening' [1], while subsequent NINDS studies defined symptomatic intracranial hemorrhage (SICH) as 'any CT-documented hemorrhage that was temporally related to deterioration in the patient's clinical condition in the judgment of the clinical investigator' [2].

Due to the high frequency of clinically irrelevant cerebral hemorrhage after intravenous thrombolysis, an additional criterion to quantify the extent of clinical deterioration was adopted by investigators of the Prolyse for Acute Cerebral Thromboembolism (PROACT) II study [3], the European Cooperative Acute Stroke Study (ECASS) [4–6] and the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) [7] studies; a 4-point change in the National Institute of Health stroke scale (NIHSS) was thought unlikely to be explained by random fluctuation in scoring between investigators. By comparison, investigators of Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) distinguished between 'minor' symptomatic hemorrhage (patients with a 2- to 3-point increment in the NIHSS) and 'major' hemorrhage (patients with ≥4-point increment) [8].

Although both the NINDS and the ECASS studies distinguished cerebral hemorrhage according to petechial (isolated or confluent) and hematoma patterns, these neuroimaging criteria differed by the inclusion of mass effect in the ECASS but not in the NINDS studies [2, 6]. The NINDS, SITS-MOST and DEFUSE definitions considered hemorrhages attributable to thrombolysis when they occurred within 36 h [2, 7, 9, 10], while ECASS II considered hemorrhages to be of clinical importance when they occurred within 7 days of intravenous thrombolysis [5]. There is an increasing trend for trials and studies to report multiple SICH rates using different definitions (tables 1–3).

We performed a systematic review to compare the incidence of SICH following intravenous thrombolysis in selected randomized clinical trials, stroke registries and cohort studies, and to appraise the criteria used to define SICH in relation to the mortality rates reported in the literature.

Methods

Search Strategy and Selection Criteria

Studies were identified from the PubMed and Embase databases from January 1994 to July 2011 by cross-referencing the following MeSH terms: 'thrombolysis', 'recombinant tissue plasminogen activator', 'rtPA', 'hemorrhagic stroke', 'cerebral hemorrhage', 'hematoma' and 'ischemic stroke'. Further studies were identified from the reference lists, related articles and citation lists of each of the papers identified in the initial searches. We included major randomized controlled trials, stroke registries and cohort studies with designs that allowed a calculation of age, baseline NIHSS scores, interval between stroke onset and intravenous thrombolysis, SICH and mortality rates. Our selection was restricted to stroke registries and larger cohort studies that comprised consecutively recruited stroke patients with an operational cutoff of >200 patients. Studies that included patients treated endovascularly and that applied preselection criteria (e.g. the presence of demonstrable arterial occlusion and availability of pretreatment MRI), and which did not report both SICH and mortality rates, were excluded. Only papers published in English were included.

Data Extraction

Two authors (R.C.S.S. and A.A.R.) performed the data search and quality assessment independently and completed a data extraction form. The case definitions used to define SICH, in terms of neurological decline, neuroimaging criteria and interval between intravenous thrombolysis and development of SICH, were analyzed.

Statistical Analysis

The mean age, baseline NIHSS scores and time from stroke onset to intravenous thrombolysis were computed for each study. The SICH and mortality rates for these studies were pooled by the use of a random-effects binomial meta-analysis; random-effects models were used because of heterogeneity in the incidence between studies. To study sources of heterogeneity of incidence, subgroup analyses and binomial metaregression were performed. Mortality rates were considered as the percentage of patients treated with intravenous thrombolysis who died within 90 days after stroke. The proportion of patients with poor functional recovery could not be computed due to the lack of standardized cutoffs used to define good and poor stroke outcomes. We compared the correlation coefficients between SICH and mortality rates to assess the consistency of SICH across these studies. Summary data from studies that defined SICH using either the SITS-MOST, ECASS or NINDS criteria were pooled to separately compare the mean, standard deviation (SD) and variance of SICH rates according to these criteria. Using mean values of these pooled data, a conversion factor of SICH rates was calculated by considering the ratios of the 'target' and 'original' case definitions of SICH. SPSS 17.0 software (SPSS Inc., Chicago, Ill., USA) was used for all statistical analyses, except for the random-effects binomial regression, for which SAS 9.1 (SAS Institute Inc., Cary, N.C., USA) was used.
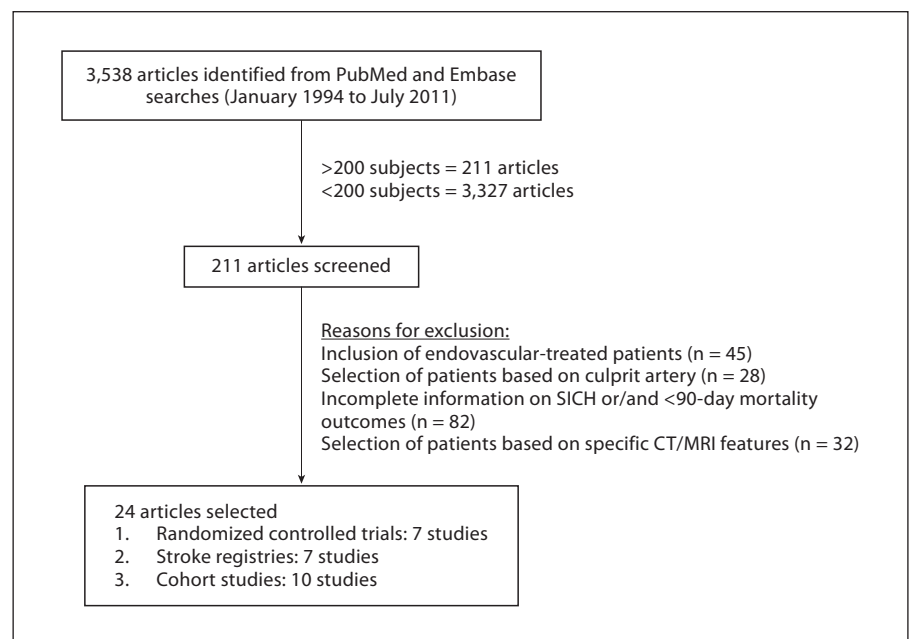
Table 1. Randomized controlled trial data of stroke patients treated with intravenous recombinant tissue plasminogen activator

Study, publication year	TPA subjects, n	Age years	Men %	Median baseline NIHSS	Time to treatment, min	SICH rates, %	Mortality rates, %
NINDS, 1995 [2]	312	68	57	14	NA	6.4[a]	17.0[f]
ECASS, 1995 [4]	313	65	60	12	NA	NA	22.4[f]
ECASS II, 1998 [5]	409	68	61	11	NA	8.8[b]	10.6[f]
ATLANTIS, 1999 [11]	547	66	55	11	276	7.0[c]	11.0[f]
DEFUSE, 2006 [8]	74	71	45	11	328	9.5[d]	NA
EPITHET, 2008 [12]	51	72	60	14	297	7.7[e]	25.0[f]
ECASS III, 2008 [6]	418	65	63	9	239	SITS-MOST 1.9; ECASS II 5.3; ECASS III 2.4; NINDS 7.9	8.0[f]
Total, mean	2,124	68 (3)	57 (5)	12 (1)	285 (37)	7.5 (1.5)[g]	15.7 (6.9)

Data are summarized as mean or median and values in parentheses indicate SD. TPA = Tissue plasminogen activator; ATLANTIS = Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; EPITHET = Echoplanar Imaging Thrombolysis Evaluation Trial; NA = not available.
[a] NINDS criteria (any neurologic decline, any cerebral hemorrhage and <36 h following intravenous thrombolysis). [b] ECASS II criteria (any neurologic decline, clinical worsening or NIHSS decline ≥4, any cerebral hemorrhage and <7 days following intravenous thrombolysis). [c] Not available. [d] DEFUSE (NIHSS decline ≥2, any cerebral hemorrhage and <36 h following intravenous thrombolysis). [e] SITS-MOST (NIHSS decline ≥4, parenchymal hemorrhage type 2 and <36 h following intravenous thrombolysis). [f] 90 days after stroke. [g] ECASS II data were used in studies that reported >1 SICH rates.

Fig. 1. Literature search and selection of studies.

Results

Study Identification and Selection

The initial search identified 3,538 nonduplicate studies which were reduced to 211 potentially eligible studies that were relevant to our investigation (fig. 1). After the application of the exclusion criteria, 7 clinical trials [2, 4–6, 8, 11, 12], 7 stroke registries [7, 9, 10, 13–16] and 10 cohort studies (4 multicenter [17–20] and 6 single-center [21–25]) were included in this analysis. Tables 1–3 describe the study population, baseline stroke severity, stroke onset to treatment time, SICH and mortality rates

Table 2. Registry data of stroke patients treated with intravenous recombinant tissue plasminogen activator

Study, publication year	TPA subjects, n	Age years	Men %	Median baseline NIHSS	Time to treatment, min	SICH rates, %	Mortality rates, %
STARS, 2000 [13]	389	69	55	13	164	3.3[a]	13.0[d]
CASES, 2005 [14]	4,468	73	55	14	155	4.6[b]	22.3[e]
SITS-MOST, 2007 [7]	6,483	68	60	12	136	SITS-MOST 1.7; ECASS 4.6 ECASS II 8.8; NINDS 7.3	11.2[e]
SITS-ITSR, 2008 [9]	12,529	68	61	12	143	SITS-MOST 1.6; ECASS 4.8 NINDS 7.3	12.1[e]
SITS-ITSR, 2010 [10]	23,942	68	60	12	146	SITS-MOST 1.75; ECASS 4.85; NINDS 7.13	12.3[e]
GWTG, 2011 [15]	25,504	70	51	12	129	5.4[a]	9.9[f]
Canadian Stroke Network, 2011 [16]	1,739	75	51	12	145	5.9[c]	16.3[f]
Total, mean	15,054	70 (3)	56 (4)	12 (1)	145 (12)	3.5 (1.8)[g]	13.9 (4.2)

Data are summarized as mean or median and values in parentheses indicate percentages. TPA = Tissue plasminogen activator; STARS = Standard Treatment with Alteplase to Reverse Stroke study; SITS-ITSR = Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register; GWTG = Get With The Guidelines.

[a] Not available. [b] Defined as any neurologic decline, parenchymal hematoma and duration <24 h after intravenous thrombolysis. [c] Defined as any neurologic decline, cerebral hemorrhage and <36 h after intravenous thrombolysis. [d] 30 days after stroke. [e] 90 days after stroke. [f] In hospital. [g] ECASS II data were used in studies that reported >1 SICH rates.

following intravenous thrombolysis in these studies. As expected, stroke registries included the largest number of patients compared with randomized controlled trials and cohort studies. The mean age of patients was 68.8 years (SD 2.9, range 63–75), of whom 56.3% (SD 4.5, range 45–63) were men. These patients presented with baseline NIHSS of 12.5 (SD 1.4, range 9–15) and received intravenous thrombolysis 175 min (SD 62, range 120–328) from stroke onset (tables 1–3).

Although several randomized studies had a central adjudication process to assign SICH in patients with cerebral hemorrhage [5, 6, 8], the decision to ascribe SICH was left to the discretion of individual investigators in the majority of the studies [2, 11, 12]. Among stroke registries, only one national registry, the Canadian Alteplase for Stroke Effectiveness Study (CASES), included central adjudication of SICH [14], and one cohort study had central adjudication of patients with suspected SICH [24]. Details of the change in the NIHSS before and after the onset of SICH were not provided in these studies. Four studies reported the mortality rates associated with SICH (mean 67.4%, range 54–79) [13, 14, 17, 24]. Depending on the criteria used to define SICH, the mortality rate of patients with SICH ranged from 42 to 62%; the mortality rate was higher when SICH was defined using the SITS-MOST criteria and lower when defined using the NINDS criteria [24].

Case Definitions of Neurological Decline

Each of the randomized clinical trials listed in table 1 employed unique case definitions of SICH [2, 4–6, 8, 11, 12]. The ECASS II [5], ECASS III [6], DEFUSE [8] and EPITHET [12] trials specified the extent of neurological decline that needed to be present before a hemorrhage was considered to be 'symptomatic', while the NINDS trial did not provide such specification [2]. The methods of SICH ascertainment were not elaborated in the ECASS [4] and ATLANTIS [11] studies. On the other hand, the ECASS III trial reported the incidence of SICH using the different definitions adopted by the SITS-MOST, ECASS II, ECASS III and NINDS studies [6].

Similarly, stroke registries and cohort studies differed in their definitions of SICH. Both CASES [14] and the Canadian Stroke Network [16] did not specify the extent of neurological decline for a hemorrhage to be considered symptomatic, while the SITS-MOST [7] and SITS-ITSR studies [9, 10] required an NIHSS decline ≥4 points to qualify as SICH. The methods of SICH determination were not explicit in the STARS [8] and GWTG [15] studies. In patients with cerebral hemorrhage, several cohort studies specified NIHSS decline ≥4 points to indicate significant neurological deterioration [19, 21, 25, 26], while others considered any form of neurological decline to be significant [22, 23]. To date, only the SITS-MOST [7] and SITS-ITSR [9, 10] registries and two cohort stud-

Table 3. Cohort data of stroke patients treated with intravenous recombinant tissue plasminogen activator

Study, publication year	TPA subjects, n	Age years	Men %	Median baseline NIHSS	Time to treatment, min	SICH rates, %	Mortality rates, %
Tanne et al., 2002 [17]	1,205	67	56	NA	NA	6.0[a]	13.5[f]
Schenkel et al., 2003 [18]	250	63	60	14	141	8.8[a]	17.0[g]
Berrouschot et al., 2005 [19]	228	68	61	14	NA	2.6[b]	7.9[g]
Chao et al., 2010 [20]	241	66	60	15	139	SITS-MOST 3.7; ECASS 5.4; NINDS 7.9	10.0[g]
Grotta et al., 2001 [21]	269	68	52	14	137	5.6[c]	15[h]
Ringleb et al., 2007 [22]	468	71	57	13	148	5.5[a]	16[g]
Sobesky et al., 2007 [26]	450	66	62	11	135	4[d]	11[g]
Uyttenboogaart et al., 2008 [23]	252	68	54	12	174	5.2[e]	17[g]
Seet et al., 2011 [25]	212	74	50	13	141	7.9[b]	20[h]
Strbian et al., 2011 [24]	985	71	54	9	120	SITS-MOST 2.1; ECASS II 7.0 NINDS 9.4	10.2[g]
Total, mean	4,455	68 (3)	56 (4)	13 (2)	146 (18)	5.9 (1.8)[i]	14.7 (4.2)

Data are summarized as mean or median and values in parentheses indicate percentages. TPA = Tissue plasminogen activator; STARS = Standard Treatment with Alteplase to Reverse Stroke study; SITS-ITSR = Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register; GWTG = Get With The Guidelines.

[a] Not available. [b] Defined as any neurologic decline, parenchymal hematoma and duration <24 h after intravenous thrombolysis. [c] Defined as any neurologic decline, cerebral hemorrhage and <36 h after intravenous thrombolysis. [d] 30 days after stroke. [e] 90 days after stroke. [f] In hospital. [g] ECASS II data were used in studies that reported >1 SICH rates.

ies [20, 24] reported SICH rates using more than one case definition.

Case Definitions of Cerebral Hemorrhage

The NINDS, ECASS and DEFUSE studies considered any new cerebral hemorrhage to be significant in their definition of SICH [2, 4–6, 8], while the SITS-MOST and SITS-ITSR studies considered only patients with parenchymal hemorrhage type 2 [7, 9, 10] to be significant. Among the stroke registries, CASES considered only those with parenchymal hemorrhage [14] while the Canadian Stroke Network included patients with any cerebral hemorrhage following intravenous thrombolysis [16]. In several cohort studies, the presence of any hemorrhage after intravenous thrombolysis has been reported without accompanying details on neurological decline [19, 21–23, 25, 26]. Although CT imaging was used to diagnose cerebral hemorrhage in a majority of these studies, both DEFUSE and EPITHET studies incorporated MR imaging in the evaluation of stroke patients with cerebral hemorrhage [8, 12]. In the majority of the randomized controlled trials, neuroimaging assessors were blinded to the clinical outcomes [2, 5, 6, 8, 12]; this rigor, however, was adopted in only 1 stroke registry [14] and 2 cohort studies [24, 25].

Interval between Intravenous Thrombolysis and Cerebral Hemorrhage

Among randomized controlled trials, the ECASS II study reported any cerebral hemorrhage as that within 7 days of intravenous thrombolysis [2], while the DEFUSE and SITS-MOST studies reported hemorrhages as those diagnosed within the first 36 h after thrombolysis [5, 6, 8, 12]. Although patients in the NINDS study were followed for up to 10 days, the interval used for its primary analysis was 36 h [2]. Stroke registries such as CASES, however, used a time interval of 24 h [14], while the Canadian Stroke Network and SITS-MOST and SITS-ITSR studies considered hemorrhages that occurred within 36 h to be associated with intravenous thrombolysis [7, 9, 10, 16]. Similar differences exist in the cohort studies, where hemorrhages occurring <36 h [19, 22, 23] and <48 h [23] following thrombolysis were considered to be causally linked to intravenous thrombolysis.

Incidence of SICH and Mortality Rates

The mean incidence of SICH following intravenous thrombolysis was 5.6 % (SD 2.3) and the mean poststroke mortality rate was 14.7 % (SD 4.8). Significant differences were observed in the incidence of SICH according to the study design; higher rates were reported in randomized

Table 4. Comparison of mean and SD of symptomatic intracranial hemorrhage rates (defined according to the SITS-MOST, ECASS and NINDS criteria) among stroke patients following intravenous thrombolysis

	Mean SICH rates, %	SD, %	Difference from mean SICH rates (%)
SITS-MOST criteria [5–7, 9, 10, 12, 20, 21, 24]	3.25	2.27	
ECASS criteria [5–7, 9, 10, 19, 20, 24, 25]	5.67	1.15	
NINDS criteria [2, 6, 7, 9, 10, 20, 24]	7.61	0.94	

Studies that reported SICH rates using either the SITS-MOST, ECASS or NINDS criteria were selected to calculate the mean values, SD and variance in SICH rates. Several studies [references 6, 7, 9, 10, 20, 24] reported SICH rates using all three criteria. Figures in the far right column illustrate the spread of SICH values from the calculated mean values.

controlled trials (mean 7.45%) and lower rates were reported in stroke registries (mean 3.5%). These differences, however, were not observed in the mortality rates of patients following intravenous thrombolysis across different study designs (online suppl. fig. 1A, B). In studies that reported SICH using different criteria [6, 7, 9, 10, 20, 24], there was a trend towards lower rates when SICH was defined using the SITS-MOST criteria compared with those studies that employed the NINDS criteria.

A lower incidence but a higher variability in SICH rates was observed across studies that employed the SITS-MOST criteria whilst lower variability was found when SICH rates were reported using the NINDS criteria (table 4). Using mean values of SICH from studies that reported SICH rates according to divergent criteria, conversion factors between SICH rates across various case definitions were calculated and summarized in online supplementary table 2. To assess the consistency of the different criteria used to define SICH, we compared the SICH and mortality rates across studies. Overall, a moderate correlation was observed between the incidence of SICH and mortality in patients treated with intravenous thrombolysis (r = 0.401, p = 0.050; online suppl. fig. 1C). The strengths of this relationship vary considerably across studies (online suppl. fig. 1D). Studies that incorporated the use of two or more of these criteria reported a higher consistency between SICH and mortality rates (table 5). Studies that defined SICH according to (1) parenchymal hemorrhage, (2) neurological decline NIHSS ≥4 and (3) occurring within 36 h of intravenous thrombolysis had a greater consistency of association between SICH and mortality rates (table 5).

Table 5. Correlational analysis between components of SICH criteria and <90-day mortality rates after stroke

	Correlation coefficient r	p values
Clinical criteria		
Any (n = 9 studies)	–0.933	0.001
NIHSS decline ≥4 (n = 20 studies)	0.431	0.084
Neuroimaging criteria		
Any (n = 20 studies)	0.257	0.320
Parenchymal hemorrhage (n = 9 studies)	0.622	0.100
Time criteria		
<36 h (n = 21 studies)	0.434	0.072
<7 days (n = 4 studies)	–0.977	0.023
Number of criteria fulfilled[a]		
1 criterion (n = 4 studies)	–0.917	0.085
2 criteria (n = 11 studies)	0.467	0.205
3 criteria (n = 7 studies)	0.631	0.128

[a] Either (1) NIHSS decline ≥4, (2) parenchymal hemorrhage or (3) time <36 h following intravenous thrombolysis.

Discussion

SICH is a devastating complication of intravenous thrombolysis treatment that is associated with high mortality. Our study highlights two important observations: (1) the incidence of SICH following intravenous thrombolysis treatment varies considerably across stroke studies and according to the criteria used to define SICH, and (2) these differences resulted in marked inconsistencies between SICH and mortality rates. Data from this review suggest that the highest consistency was observed in the cohort studies and in the studies that defined SICH as

parenchymal hemorrhage associated with NIHSS increments of ≥4 points occurring within 36 h of intravenous thrombolysis. To our knowledge, this is the first systematic review that assesses the incidence of SICH among patients treated with intravenous thrombolysis. Previous narrative reviews [27–29] focused on data derived from randomized controlled trials and one meta-analysis included patients treated outside of the setting of clinical trials [30].

What is considered to be significant neurological decline differs across studies. The NINDS and ECASS II criteria considered any neurological decline to be significant, thus allowing for the inclusion of patients with mild and transient neurological worsening, which is fairly prevalent in the first couple of days after a stroke. Although the use of clinical severity scores to quantify the extent of neurological deterioration (e.g. NIHSS ≥4) provides an objective assessment of hemorrhage severity, this method is limited by the 'ceiling effects' associated with these scores; patients with severe strokes and high baseline NIHSS scores may not exhibit a further increase in scores despite a significant hemorrhage. The determination of SICH using these quantitative criteria is demanding as it requires close (sometimes hourly) monitoring of NIHSS scores to identify patients at the onset of neurological decline, thus limiting its use to studies performed prospectively. Despite these technical considerations, the use of quantitative scoring to define neurological decline has been reported retrospectively in several studies [31, 32]. Furthermore, in patients with an insidious and progressive course of deterioration, such baseline levels may be difficult to establish. In ECASS II, when doubts arose as to whether edema or hemorrhage was the leading pathology, an association of the hemorrhage was assumed [5], whereas in ECASS III, adjudication of the cause of death or neurological decline (attributed to intracranial hemorrhage, other brain injury or neither of these causes) was performed by the chairs of the safety outcome adjudication committee and the steering committee [6].

Investigators of CASES have previously highlighted that not all sizable hemorrhages result in symptoms [33]. Massive bleedings into noneloquent areas of the brain may be asymptomatic or only slightly symptomatic (though these may potentially have an impact on the eventual chances of favorable functional recovery). These same bleedings (albeit small) may be symptomatic in strokes affecting a dominant cerebral hemisphere. Accumulating data indicate that the pattern and size of the hemorrhage, as well as associated features such as cerebral edema, may be important in SICH determination [4–6]. The distinction of cerebral hemorrhages between hemorrhagic infarctions and parenchymal hemorrhages is pertinent because parenchymal hemorrhages that exceed 30% of the infarcted area with space-occupying effect are associated with increased risks of early neurological deterioration and higher 3-month mortality [34]. By contrast, although smaller hemorrhages do not generally have an impact on functional recovery, petechiae that are more confluent (termed 'HI2') are associated with worse stroke outcomes [34].

Several studies such as EPITHET and DEFUSE used CT and MRI scans interchangeably to report cerebral hemorrhage [8, 12]. Despite data to suggest lower SICH and mortality rates in stroke patients selected for intravenous thrombolysis using MRI compared with CT modalities [35], the superiority of MR-based imaging has not been prospectively studied. It is not known whether the presence of leukoaraiosis and microbleeds detected on pretreatment MRI has any significance for SICH risks, and whether the more accurate characterization of hemorrhages afforded by sensitive imaging methods such as the gradient-recalled echo and the susceptibility-weighted imaging following intravenous thrombolysis have prognostic implications on hemorrhage risks and outcomes. Occasionally, retention of contrast may cause CT hyperdensity and changes on MRI such as T_1-weighted hyperintensity, obscuring a clear distinction between cerebral hemorrhage and contrast staining following arterial recanalization.

The interval for SICH to be considered causally linked to intravenous thrombolysis varies across studies, ranging from <24 h [14], <36 h [5–10, 12, 16, 19, 20, 22, 25], <48 h [23] and <7 days [2, 6, 7, 9, 10, 20]. Studies that report SICH according to the SITS-MOST criteria tended to report lower hemorrhagic rates compared to those that employed the ECASS criteria [6, 7, 9, 10, 20, 24]. Despite manifesting initially as hemorrhagic infarctions, these hemorrhages may coalesce and transform into a parenchymal-type hemorrhage. An interval development of sepsis, cerebral edema and recurrent stroke may confound the assessment of neurological function associated with these hemorrhages. It is noteworthy that none of the studies included in this review reported the precise interval between intravenous thrombolysis and SICH development. This temporal information may be pertinent to determine causality, as cerebral hemorrhages that occur early are more likely to be attributed to intravenous thrombolysis compared to those that occur later. The variability in SICH rates (reported using different case

definitions) may explain certain inconsistencies between SICH and mortality rates. Across the wide range of SICH definitions reported, the SICH rate explains only about one-sixth of the variation in mortality in recombinant tissue plasminogen activator-treated stroke patients. In ECASS III (the only randomized placebo-controlled study that reported SICH rates using different case definitions), fewer patients with cerebral hemorrhage in the placebo group were considered to have SICH when SICH was defined by ECASS III and SITS-MOST criteria (both 0.2%) compared to ECASS II and NINDS criteria (2.2 and 3.5%, respectively). These findings highlight inherent limitations of existing case definitions in describing thrombolysis-related hemorrhage.

Our study has several limitations. First, eligible articles were restricted to studies published in English and conference abstracts were not accessed. This may have resulted in the inadvertent exclusion of relevant studies in the non-English literature and unpublished data. Second, only cohort studies with >200 consecutive stroke patients were included and this inclusion criteria may have resulted in a selection of high-volume and experienced stroke centers. Third, to ensure uniformity in patient selection, only studies that included patients who received intravenous thrombolysis were chosen while those that reported patients undergoing endovascular treatment were excluded. Fourth, information included in this study was based on the published data; raw data were not available for analysis. It remains possible that these findings are in part due to a sampling error since small incidences are inevitably prone to greater variation.

This systematic study highlights several inconsistencies in the criteria used to define SICH. There is a pressing need for investigators to agree on the clinical, radiological and time interval criteria that should be used to define SICH and to standardize methods employed to report these outcomes. Until a case definition with a high inter-rater agreement rate and good correlation with clinical outcomes becomes available, information on the type of bleeding, the extent of NIHSS deterioration and the time interval between thrombolysis and bleeding should be reported to allow correct interpretation of SICH rates.

Disclosure Statement

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