ORIGINAL RESEARCH

Predictors and clinical relevance of hemorrhagic transformation after endovascular therapy for anterior circulation large vessel occlusion strokes: a multicenter retrospective analysis of 1122 patients

Raul G Nogueira,[1] Rishi Gupta,[1] Tudor G Jovin,[2] Elad I Levy,[3] David S Liebeskind,[4] Osama O Zaidat,[5] Ansaar Rai,[6] Joshua A Hirsch,[7] Daniel P Hsu,[8] Marilyn M Rymer,[9] Ashis H Tayal,[10] Ridwan Lin,[2] Sabareesh K Natarajan,[3] Ashish Nanda,[3] Melissa Tian,[10] Qing Hao,[4] Junaid S Kalia,[5] Michael Chen,[11] Alex Abou-Chebl,[12] Thanh N Nguyen,[13] Albert J Yoo[7]

For numbered affiliations see end of article.

Correspondence to
Dr R Gupta, Emory University School of Medicine, 49 Jesse Hill Dr SE, Room 393, Atlanta, GA 30303, USA;
rishi.gupta@emory.edu

Received 1 October 2013
Revised 13 December 2013
Accepted 15 December 2013
Published Online First
8 January 2014

ABSTRACT

Background and purpose Endovascular techniques are frequently employed to treat large artery occlusion in acute ischemic stroke (AIS). We sought to determine the predictors and clinical impact of intracranial hemorrhage (ICH) after endovascular therapy.

Methods Retrospective analysis of consecutive patients presenting to 13 high volume stroke centers with AIS due to proximal occlusion in the anterior circulation who underwent endovascular treatment within 8 h from symptom onset. Logistic regression was performed to determine the variables associated with ICH, hemorrhagic infarction (HI), and parenchymal hematomas (PHs), as well as 90 day poor outcome (modified Rankin Scale score ≥3) and mortality.

Results There were a total of 363 ICHs (overall rate 32.3%; HI=267, 24%; PH=96, 8.5%) among the 1122 study patients (mean age 67±15 years; median National Institutes of Health Stroke Scale score 17 (IQR 13–20)). Independent predictors for HI included diabetes mellitus (OR 2.27, 95% CI (1.58 to 3.26), p<0.0001), preprocedure IV tissue plasminogen activator (tPA) (1.43 (1.03 to 2.08), p<0.037), Merci thrombectomy (1.47 (1.02 to 2.12), p<0.032), and longer time to puncture (1.001 (1.00 to 1.002), p<0.026). Patients with atrial fibrillation (1.61 (1.01 to 2.55), p<0.045) had a higher risk of PH while the use of IA tPA (0.57 (0.35 to 0.90), p<0.008) was associated with lower chances of PH. Both the presence of HI (2.23 (1.53 to 3.25), p<0.0001) and PH (6.24 (3.06 to 12.75), p<0.0001) were associated with poor functional outcomes; however, only PH was associated with higher mortality (3.53 (2.19 to 5.68), p<0.0001).

Conclusions Greater understanding about the predictors and consequences of ICH post endovascular stroke therapy is essential to improve risk assessment, patient selection/clinical outcomes, and early prognostication. Our data suggest that patients with atrial fibrillation are particularly prone to severe ICH and question the 'benign' nature of HI suggested by earlier studies.

To cite: Nogueira RG, Gupta R, Jovin TG, *et al*. *J NeuroIntervent Surg* 2015;**7**:16–21.

Intracranial hemorrhage (ICH) is a potentially catastrophic complication after reperfusion therapies for treatment of acute ischemic stroke (AIS). This complication has been linked to the use of, and dosage of, thrombolytic drugs, advanced age, increased time to treatment, higher baseline National Institutes of Health Stroke Scale (NIHSS) score, high systolic blood pressure, hyperglycemia, diabetes mellitus, pretreatment involvement of the basal ganglia, and the extent of ischemic injury prior to administration of therapy.[1 2]

The definition of a symptomatic ICH (SICH) after reperfusion therapy has not been standardized.[2–5] A recent study demonstrated that none of the four most commonly applied definitions of SICH after stroke thrombolysis (eg, National Institute of Neurological Disorders and Stroke (NINDS), European Cooperative Acute Stroke Study (ECASS) 2, Safe Implementation of Thrombolysis in Stroke (SITS), and ECASS 3) comprises an optimal combination of prediction of mortality/outcome and a high inter-rater agreement rate, and suggested that future trials should use multiple definitions.[3] There are many factors that may prevent a precise determination of the clinical implications of ICH. In patients with large territory infarcts, neurologic decline may also occur due to superimposed malignant edema. Many patients with severe strokes, and in particular the ones who undergo endovascular therapy, may be placed on mechanical ventilation and the inconsistent examination in this setting may be misconstrued as a true neurologic deterioration. The more recent SICH definitions employed in the SITS Registry[6] and ECASS III trial[7] require adjudication of the cause of neurological deterioration allowing for adjustments for other causes of clinical decline, such as early cerebral edema, fever, hypoxemia, sedation, and other systemic conditions.

Better understanding of the factors that predispose to SICH may allow for better treatment selection and improved outcomes. Greater knowledge about the consequences of SICH may assist with early prognostication and establishing goals of care. Three prediction models to estimate the risk of SICH after IV thrombolysis have been recently proposed and validated.[8–10] These studies have

identified age, baseline NIHSS, systolic blood pressure, blood glucose, Asian race, male gender, body weight, stroke onset to treatment time, use of aspirin or combined aspirin and clopidogrel, and admission CT findings, including early infarct signs and hyperdense cerebral artery sign, as the most powerful predictors. However, there is a paucity of data about the predictors and consequences of SICH in patients treated with endovascular therapy.

The ECASS classification has been utilized for grading post-treatment hemorrhages where hemorrhagic infarction type 1 (HI-1) reflects small petechiae, HI-2 confluent petechiae, parenchymal hematoma type 1 (PH-1) hematoma that is less than 30% of the infarcted area, and PH-2 where the hematoma is greater than 30% of the infarcted area with a significant space occupying effect.[11] This definition has been more widely adopted for acute stroke treatment as it may better reflect the causal association between hemorrhage and poor outcome—that is, if patients develop a PH-type bleed.[2] We reviewed a multicenter clinical experience of the predictors of hemorrhagic transformation (HT) according to the ECASS classification (HI and PH) and sought to determine the impact of these bleeding types on clinical outcomes following endovascular therapy.

METHODS

This retrospective analysis was approved by the institutional review board from each of the 13 participating institutions as well as the coordinating institution to assess predictors and clinical impact of ICH associated with endovascular therapy for AIS. Each site completed a data collection sheet consisting of demographic variables (de-identified), baseline (preprocedural) NIHSS scores, IV tissue plasminogen activator (tPA) usage, location of thrombus within the intracranial cerebral circulation (including tandem occlusions), technical aspects of the procedure (devices and pharmacologic agents used), Thrombolysis in Myocardial Infarction (TIMI) recanalization grade, postprocedural hemorrhage, and 90 day outcomes. Multimodal therapy was defined as the use of a mechanical device in conjunction with a pharmacologic agent (administered IV and/or IA). Inclusion criteria for this analysis were: (1) AIS involving the proximal anterior circulation (internal carotid artery and/or middle cerebral artery (MCA) M1 or M2 segments); (2) endovascular therapy within 8 h from symptom onset with available post-treatment recanalization grade; (3) follow-up imaging for hemorrhage grading; and (4) 90 day clinical outcome. Patients with posterior circulation strokes and those in whom IA therapy was not performed (spontaneous or IV tPA induced recanalization) were not included in the analysis. A total of 1122 patients met the inclusion criteria. Three month follow up was available in 1033 patients.

A post-treatment TIMI score of 2 or 3 was defined as successful recanalization. Cerebral hemorrhages were classified as HI or PH based on previously published guidelines.[11] Hemorrhage was distinguished from contrast staining by assessing for clearance of the hyperdensity on the 24–36 h post treatment CT scan or by means of brain MRI gradient echo sequence. Recanalization grades and hemorrhages were classified by experienced neuroradiologists, stroke neurologists, or neurointerventionists at each individual center. None of the centers relied on radiology reports. All CT and MRI scans were reviewed by a study investigator with proper training and knowledge about the ECASS ICH classification. Poor functional outcome was defined as a modified Rankin Scale score of ≥3 at 90 days.

Statistical analysis

A univariate analysis was performed using Fisher's exact test for categorical variables and the Student's t test for continuous variables to identify predictors of HI and PH. A binary logistic regression was then constructed using variables with a p value <0.20 to determine independent predictors of HI and PH. A binary logistic regression model was also constructed to determine predictors of outcomes in a similar manner as previously described.[12] Analysis was performed using SPSS V.10.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

A total of 1122 patients met the inclusion criteria for this study. Mean age for the cohort was 67±15 years with a median NIHSS score of 17 (IQR 13–20). Of these patients, 52% were women, 69% were known to have hypertension, 24% were diabetic, and 39% had a history of atrial fibrillation. The distribution for thrombus location was as follows: MCA-M1 segment 560 (50%), carotid terminus 214 (19%), MCA-M2 172 (15%), tandem occlusions 141 (13%), and isolated extracranial internal carotid artery occlusion 35 (3%). A total of 371 patients (33%) received IV tPA prior to endovascular therapy. Successful recanalization was achieved in 69% of patients, with 37% of all patients achieving a good outcome. The mean time from symptom onset to recanalization was 422±286 min. The overall mortality rate was 30%. PHs occurred in 96 (8.5%) patients and HI in 267 (24%) patients.

Tables 1 and 2 summarize the univariate and multivariate analysis of predictors of any ICH. Table 3 summarizes the univariate analysis of predictors of HI. Higher baseline NIHSS, history of diabetes mellitus, longer time from symptom onset to arterial puncture, IV tPA, and use of Merci thrombectomy device were associated with a higher risk for HI. Occlusion of the M2 MCA segment was associated with a lower risk for HI. Table 4 summarizes the binary logistic regression model for predictors of HI. Diabetes mellitus (OR 2.27 (1.58 to 3.26), p=0.0001), longer time from symptom onset to puncture (OR 1.001 (1.00 to 1.002), p=0.026), and use of Merci thrombectomy (OR 1.47 (1.02 to 2.12), p=0.032) were independent predictors of HI.

In univariate modeling for predictors of PH (table 5), higher baseline NIHSS score, history of atrial fibrillation, and use of mechanical therapy without any pharmacological adjunctive therapy were found to be associated with a higher likelihood of PH while the use of any IA tPA and the use of pharmacological therapy only were inversely associated with the development of PH. In binary logistic regression modeling (table 6), atrial fibrillation (OR 1.61 (1.01 to 2.55), p=0.045) was an independent predictor of PH while the use of IA thrombolytics (OR 0.57 (0.35 to 0.90), p=0.008) was independently associated with a lower chance of PH. Higher baseline NIHSS showed a strong trend towards a higher chance of PH (OR 1.04 (0.999 to 1.08), p=0.056).

Interestingly, patients with ICH had similar recanalization rates to patients without ICH. Specifically, there was no significant difference in terms of postprocedural TIMI 2–3 recanalization rates according to the presence or absence of any ICH (68% vs 68%, p=0.89), any HI (67% vs 69%, p=0.38), or any PH (70% vs 68%, p=0.81).

After controlling for age, baseline NIHSS, recanalization status, type of sedation, and site of occlusion, both the presence of HI (OR 2.23 (1.53 to 3.25), p<0.0001) and PH (OR 6.24 (3.06 to 12.75), p<0.0001) were associated with poor functional outcomes (90 day modified Rankin Scale score ≥3);

Table 1 Univariate analysis of predictors of any intracranial hemorrhage after endovascular stroke therapy

Variable	Any intracranial hemorrhage (n=363) (N (%))	No hemorrhage (n=759) (N (%))	p Value
Demographics			
Age (years) (mean ±SD)	67±15	66±15	0.49
NIHSS (mean±SD)	17±5	16±6	0.001
Female	174 (48)	366 (48)	0.94
Diabetes mellitus	109 (30)	156 (20)	0.0001
Hypertension	255 (71)	518 (68)	0.53
Atrial fibrillation	148 (41)	265 (35)	0.05
Time to treatment (min) (mean±SD)	312±157	296±162	0.15
TIMI 2–3 recanalization	247 (68)	520 (69)	0.89
Clot location			
M1 MCA	192 (53)	369 (49)	0.20
Carotid terminus	72 (20)	142 (19)	0.69
Tandem occlusion	47 (13)	94 (12)	0.43
M2 MCA	43 (12)	129 (17)	0.03
Extracranial ICA	10 (3)	25 (3)	0.71
Therapy			
IV tPA	137 (38)	234 (31)	0.025
Merci embolectomy	130 (36)	233 (30)	0.002
Penumbra thrombectomy	42 (11)	88 (12)	0.82
Angioplasty	97 (27)	189 (25)	0.56
Stent placement	70 (19)	145 (19)	0.51
IA tPA	194 (53)	408 (54)	0.49
Pharmacologic therapy only	73 (20)	191 (25)	0.07
Mechanical therapy only	91 (25)	184 (24)	0.41
Multimodal therapy	199 (54)	385 (51)	0.20

ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TIMI, Thrombolysis in Myocardial Infarction; tPA, tissue plasminogen activator.

however, only PH was associated with higher 90 day mortality (OR 3.53 (2.19 to 5.68), p<0.0001).

DISCUSSION

HT can be categorized according to its clinical or radiological presentation. We have chosen a radiological scale as it is thought to be more objective and easier to employ across multiple institutions. The ECASS definition was formulated for IV thrombolysis trials and its applicability to endovascular treatment had not been previously well demonstrated. We have shown that among patients with anterior circulation stroke undergoing endovascular therapy, both HI and PH are independent predictors of poor long term functional outcome.

Table 2 Independent predictors of development of any intracranial hemorrhage after endovascular stroke therapy

Variable	OR (95% CI)	p Value
Diabetes mellitus	1.71 (1.27 to 2.30)	0.0001
Merci device	1.51 (1.05 to 2.18)	0.025
NIHSS	1.03 (1.008 to 1.059)	0.009

NIHSS, National Institutes of Health Stroke Scale.

Table 3 Univariate analysis for the predictors of the development of hemorrhagic infarction after endovascular stroke therapy

Variable	HI hemorrhage (n=267) (N (%))	No hemorrhage (n=759) (N (%))	p Value
Demographics			
Age (years) (mean ±SD)	66±16	66±15	0.95
NIHSS (mean±SD)	17±5	16±6	0.004
Female	139 (52)	393 (52)	0.94
Diabetes mellitus	88 (33)	156 (21)	0.0001
Hypertension	182 (68)	518 (68)	0.91
Atrial fibrillation	100 (37)	265 (35)	0.45
Time to treatment (min) (mean±SD)	320±161	296±162	0.05
TIMI 2–3 recanalization	180 (67)	520 (69)	0.39
Clot location			
M1 MCA	140 (52)	369 (49)	0.29
Carotid terminus	56 (21)	142 (19)	0.42
Tandem occlusion	34 (13)	94 (12)	0.91
M2 MCA	30 (11)	129 (17)	0.03
Extracranial ICA	8 (3)	25 (3)	0.50
Therapy			
IV tPA	108 (40)	234 (31)	0.005
Merci embolectomy	172 (64)	411 (54)	0.002
Penumbra thrombectomy	28 (10)	88 (12)	0.66
Angioplasty	70 (26)	189 (25)	0.68
Stent placement	49 (18)	145 (19)	0.86
IA tPA	155 (58)	408 (54)	0.22
Pharmacologic therapy only	58 (22)	191 (25)	0.28
Mechanical therapy only	57 (21)	184 (25)	0.35
Multimodal therapy	152 (57)	385 (51)	0.09

HI, hemorrhagic infarction; ICA, internal carotid artery; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TIMI, Thrombolysis in Myocardial Infarction; tPA, tissue plasminogen activator.

Our findings are somewhat contrary to conventional thinking in which HI is considered to be relatively benign. A previous study involving 32 AIS patients with proximal MCA occlusion who were treated with IV tPA within 3 h of symptom onset suggested that thrombolysis related HI is a marker of early reperfusion, reduced infarct size, and improved outcome.[13] However, a subsequent analysis involving 954 patients from the Canadian Alteplase for Stroke Effectiveness Study (CASES) Registry demonstrated that after adjustment for age, baseline serum glucose, baseline Alberta Stroke Program Early CT score (ASPECTS), and baseline NIHSS score, HI-1 was not a predictor of outcome and that HI-2 (along with PH-1 and PH-2) was actually a negative predictor of good outcome (90 day modified Rankin Scale score ≤1).[14] Similarly, we have shown that in this cohort of endovascularly treated patients, HI may actually be associated with poor clinical outcome in long term follow-up. Our findings also confirm previous studies demonstrating the greater clinical relevance of PHs, which demonstrated a greater point estimate than HI for odds of a poor outcome and was the only independent predictor of mortality.

Table 4 Independent predictors of hemorrhagic infarction after endovascular stroke therapy

Variable	OR (95% CI)	p Value
Diabetes mellitus	2.27 (1.58 to 3.26)	0.0001
Time from symptoms onset to puncture	1.001 (1.00 to 1.002)	0.026
Merci device	1.47 (1.02 to 2.12)	0.032
IV tPA prior to intervention	1.43 (1.03 to 2.08)	0.037

tPA, tissue plasminogen activator.

Table 6 Independent predictors of parenchymal hematoma after endovascular stroke therapy

Variable	OR (95% CI)	p Value
IA tPA	0.57 (0.35 to 0.90)	0.008
Atrial fibrillation	1.61 (1.01 to 2.55)	0.045
NIHSS	1.04 (0.999 to 1.08)	0.056

NIHSS, National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

Identification of patients at higher risk for SICH may allow for the early implementation of more aggressive preventive strategies (eg, tighter control of blood pressure and glucose levels as well as avoidance of aggressive antithrombotic therapy in the early post-stroke phases) and potentially lead to better outcomes. In our study, the presence of atrial fibrillation and the absence of IA thrombolytics were the only independent predictors of PH in this large cohort of 1122 patients with stroke severity (baseline NIHSS) approaching statistical significance. The Interventional Management of Stroke investigators have suggested that atrial fibrillation is a strong risk factor for HT in AIS patients treated with combined IV and IA tPA.[15] Our findings confirm this notion in this much larger cohort of AIS treated with endovascular therapy with or without preceding IV thrombolysis. Notably, lower recanalization rates have been reported after endovascular treatment of cardioembolic strokes compared with carotid embolic strokes.[16] It is important to point out that data about preprocedural antithrombotic/anticoagulation therapy were not available for many of the study centers and therefore were not included in our analysis. As such, it is possible that the higher rate of PH in atrial fibrillation patients is derived from the more frequent use of antithrombotic/anticoagulation therapy in these patients as opposed to the atrial fibrillation itself. However, a previous analysis of the Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST), where 6483 patients were treated with IV alteplase within 3 h of stroke symptom onset, has also demonstrated that atrial fibrillation is an independent predictor of symptomatic intracerebral hemorrhage. As SITS-MOST patients had an international normalized ratio of ≤1.7, this study suggests that atrial fibrillation may indeed have an effect on SICH, independent of anticoagulation.[17] The inverse relationship between PH and the use of IA thrombolytics is somewhat counterintuitive and may represent selection bias, where patients with a more favorable imaging profile would have preferably received IA thrombolytics. Interestingly, patients with ICH had similar recanalization rates to patients without ICH. This finding supports the notion that the reperfusion injury that is related to ICH is likely a delayed phenomenon as opposed to a direct consequence of intraprocedural reperfusion. Diabetes was a risk factor for ICH in our study. Patients with diabetes are noted to have higher blood sugars at the time of presentation compared with non-diabetic patients.[18] The presence of diabetes and/or hyperglycemia has been associated with a higher risk of symptomatic ICH after IV or IA thrombolysis in several previous studies.[1 2 18] We have previously demonstrated the lack of influence of the type of sedation/anesthesia on the rates of ICH. In a previous study involving a similar cohort of patients, there was no difference in the rates of HI (27% vs 24%, p<0.22) or PH (9.3% vs 9.1%, p<0.82) in patients undergoing general anesthesia versus conscious sedation, respectively.[12]

Table 5 Univariate analysis of predictors of parenchymal hematoma after endovascular stroke therapy

Variable	PH (n=96) (N (%))	No ICH (n=759) (N (%))	p Value
Demographics			
Age (years) (mean±SD)	69±14	66±16	0.09
NIHSS (mean±SD)	18±6	16±6	0.009
Female	50 (52)	393 (52)	0.85
Diabetes mellitus	21 (22)	156 (21)	0.44
Hypertension	73 (76)	518 (68)	0.09
Atrial fibrillation	48 (50)	265 (35)	0.003
Time to treatment (min±SD)	290±139	296±162	0.75
TIMI 2–3 recanalization	67 (70)	520 (69)	0.91
Clot location			
M1 MCA	52 (54)	369 (49)	0.18
Carotid terminus	16 (17)	142 (19)	0.37
Tandem occlusion	13 (14)	94 (12)	0.74
M2 MCA	13 (13)	129 (17)	0.47
Extracranial ICA	2 (2)	25 (3)	0.76
Therapy			
IV tPA	29 (30)	234 (31)	0.50
Merci embolectomy	61 (63)	411 (54)	0.05
Penumbra thrombectomy	14 (15)	88 (12)	0.25
Angioplasty	27 (28)	189 (25)	0.53
Stent placement	21 (22)	145 (19)	0.31
IA tPA	39 (41)	408 (54)	0.009
Pharmacologic therapy only	15 (16)	191 (25)	0.02
Mechanical therapy only	34 (35)	184 (24)	0.014
Multimodal therapy only	47 (49)	385 (51)	0.41

ICA, internal carotid artery; ICH, intracranial hemorrhage; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma; TIMI, Thrombolysis in Myocardial Infarction; tPA, tissue plasminogen activator.

The Merci device was associated with higher rates of HI. The use of mechanical devices that are sized to the diameter of the cerebral vessel can aid with reperfusion, but this may occur at the expense of increased vessel injury, vasospasm, or arterial dissection. Mechanical devices may cause microperforations at the time of deployment or retraction. Even though contrast extravasation at the time of the procedure is a relatively rare event, some degree of SAH is not uncommon. Indeed, a recent series demonstrated postprocedure SAH in 20 of 159 patients (12.6%; isolated SAH in eight, SAH and parenchymal hemorrhages in 12) treated with endovascular therapy.[19] In this study, patients treated with primary thrombectomy had a higher incidence of SAH than patients treated with IA thrombolysis; however, only extensive SAH or SAH accompanied by severe PH was associated with worsened clinical outcomes.

The use of IV tPA prior to treatment with mechanical devices or IA thrombolytic therapy has not been associated with higher rates of SICH compared with mechanical or pharmacologic IA

interventions in isolation. In the Multi MERCI trial, 29.3% of patients (48/164) received IV tPA before angiography. No differences in the rates of ICH or clinically significant procedural complications were observed between those patients treated with IV tPA and those who were not, suggesting that pretreatment with IV tPA does not raise a safety concern.[20] Many other studies have also suggested that pretreatment with IV tPA does not result in higher rates of SICH after AIS endovascular therapy.[21] However, more definite answers about the risks associated with combined IV and IA therapies will only come after the analysis of the Interventional Management of Stroke III Trial. The use of IV thrombolytics in conjunction with endovascular techniques may lead to higher and faster rates of recanalization. Conversely, the combination of delayed reperfusion and the potential neurotoxic effects of IV tPA potentially place these patients at a higher risk for hemorrhagic complications.[22 23] In our study, pretreatment IV tPA was an independent predictor of HI (but not PH) after endovascular stroke therapy.

There are limitations to the current study. This was a retrospective analysis of 13 centers and, consequently, the CT studies have not been adjudicated by a core laboratory. However, each center has a high level of experience with performing these procedures and many have participated in large scale clinical trials for endovascular stroke therapy. Secondly, we were not able to assess the degree and location of hypodensity on CT scan prior to or following the intervention, or the HI or PH subtypes. However, the association between higher NIHSS and ICH we have described indirectly suggests that stroke burden is associated with hemorrhagic complications as larger strokes would presumably have higher baseline NIHSS scores. Each center may have a different threshold to treat patients, but typically patients with ischemic injury in greater than a third of the MCA territory were excluded. Nonetheless, patients presenting with larger strokes, as is the case in patients being treated with endovascular therapy, have a higher predilection for HI-type bleeds.[22] It is important to mention that in two different studies, asymptomatic HT was not associated with worse outcomes after adjustment for infarct volume.[24 25] Other variables, including the use of heparin, number of trials for embolectomy, procedure duration, periprocedural blood pressure, presence of heart failure, baseline international normalized ratio, prior usage of antithrombotic agents, and degree of pial collateral flow were not assessed in the current study and could have theoretically impacted on some of our results. Given the retrospective nature of our study, there was no standardization of postprocedure care. As such, inter-site differences in postprocedure care could have had an influence on the formation of HI/PH. However, the fact that the study sites were high volume stroke centers with dedicated stroke and neurocritical care services following the American Heart Association Stroke Guidelines presumably provided some degree of homogenicity to our postprocedure care.

In conclusion, greater understanding of the predictors and consequences of ICH post endovascular stroke therapy is essential to improve risk assessment, patient selection/clinical outcomes, and early prognostication. Our data suggest that patients with atrial fibrillation are particularly prone to severe ICH and questions the 'benign' nature of HI suggested by earlier studies.

Author affiliations
[1]Emory University School of Medicine, Atlanta, Georgia, USA
[2]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA
[3]SUNY Buffalo, Buffalo, New York, USA
[4]University of California Los Angeles, Los Angeles, California, USA
[5]Medical College of Wisconsin, Milwaukee, Wisconsin, USA
[6]University of West Virginia, Morgantown, Virginia, USA
[7]Massachusetts General Hospital, Boston, Massachusetts, USA
[8]University Hospitals of Cleveland, Cleveland, Ohio, USA
[9]Saint Luke's Stroke Institute, Kansas City, Kansas, USA
[10]Allegheny General Hospital, Pittsburgh, Pennsylvania, USA
[11]Rush University Medical Center, Chicago, Illinois, USA
[12]University of Louisville Medical Center, Louisville, Kentucky, USA
[13]Boston University School of Medicine, Boston, Massachusetts, USA

Contributors RGN and RG analyzed the data and drafted the manuscript. RGN, RG, and AJY designed and conceptualized the project. All authors participated in the data gathering, meaningful editing, suggestions, and feedback on the final manuscript.

Competing interests AJY has research support from Penumbra Corp. TGJ is on the consultant/scientific advisory boards for CoAxia Medical and Stryker Neurovascular/Concentric Medical and is a consultant for Covidien/EV3. EIL has received a research grant from Boston Scientific Corp; research support from Micrus Endovascular, Abbott Vascular, and EV3; has received honoraria from Intratech Medical Ltd; has an ownership interest in Mynx/Access Closure and TheraSyn Sensors, Inc; and is on the consultant/advisory boards for Cordis Neurovascular and Micrus Endovascular. MMR is a speaker for Stryker Neurovascular/Concentric Medical and a consultant for Genentech. AHT is a speaker for Genentech and Boehringer Ingelheim. DSL and RGN are consultants to, and on the advisory boards for, Stryker Neurovascular/Concentric Medical, Covidien/EV3, and CoAxia. OZ is on the consultant/scientific advisory board for Stryker Neurovascular. MC is a speaker for Stryker Neurovascular/Concentric Medical. RG is on the consultant/scientific advisory boards for Stryker Neurovascular/Concentric Medical and CoAxia. DSL has received significant research support from the National Institutes of Health.

Ethics approval The study was approved by the local institutional review boards.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 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.
2 Khatri P, Wechsler LR, Broderick JP. Intracranial hemorrhage associated with revascularization therapies. *Stroke* 2007;38:431–40.
3 Gumbinger C, Gruschka P, Bottinger M, *et al*. Improved prediction of poor outcome after thrombolysis using conservative definitions of symptomatic hemorrhage. *Stroke* 2012;43:240–2.
4 Strbian D, Sairanen T, Meretoja A, *et al*. Patient outcomes from symptomatic intracerebral hemorrhage after stroke thrombolysis. *Neurology* 2011;77:341–8.
5 Seet RC, Rabinstein AA. Symptomatic intracranial hemorrhage following intravenous thrombolysis for acute ischemic stroke: a critical review of case definitions. *Cerebrovasc Dis* 2012;34:106–14.
6 Wahlgren N, Ahmed N, Davalos A, *et al*. Thrombolysis with alteplase 3–4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet* 2008;372:1303–9.
7 Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–29.
8 Menon BK, Saver JL, Prabhakaran S, *et al*. Risk score for intracranial hemorrhage in patients with acute ischemic stroke treated with intravenous tissue-type plasminogen activator. *Stroke* 2012;43:2293–9.
9 Mazya M, Egido JA, Ford GA, *et al*. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. *Stroke* 2012;43:1524–31.
10 Strbian D, Engelter S, Michel P, *et al*. Symptomatic intracranial hemorrhage after stroke thrombolysis: the SEDAN score. *Ann Neurol* 2012;71:634–41.
11 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.
12 Abou-Chebl A, Lin R, Hussain MS, *et al*. Conscious sedation versus general anesthesia during endovascular therapy for acute anterior circulation stroke: preliminary results from a retrospective, multicenter study. *Stroke* 2010;41:1175–9.
13 Molina CA, Alvarez-Sabin 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.
14 Dzialowski I, Pexman JH, Barber PA, *et al*. Asymptomatic hemorrhage after thrombolysis may not be benign: prognosis by hemorrhage type in the Canadian alteplase for stroke effectiveness study registry. *Stroke* 2007;38:75–9.
15 IMS Study Investigators. Hemorrhage in the Interventional Management of Stroke study. *Stroke* 2006;37:847–51.

16 Hussain MS, Lin R, Cheng-Ching E, *et al*. Endovascular treatment of carotid embolic occlusions has a higher recanalization rate compared with cardioembolic occlusions. *J Neurointerv Surg* 2010;2:71–3.
17 Wahlgren N, Ahmed N, Eriksson N, *et al*. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). *Stroke* 2008;39:3316–22.
18 Natarajan SK, Dandona P, Karmon Y, *et al*. Prediction of adverse outcomes by blood glucose level after endovascular therapy for acute ischemic stroke. *J Neurosurg* 2011;114:1785–99.
19 Shi ZS, Liebeskind DS, Loh Y, *et al*. Predictors of subarachnoid hemorrhage in acute ischemic stroke with endovascular therapy. *Stroke* 2010;41:2775–81.
20 Smith WS, Sung G, Saver J, *et al*. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke* 2008;39:1205–12.
21 Nogueira RG, Yoo AJ, Masrur S, *et al*. Safety of full-dose intravenous recombinant tissue plasminogen activator followed by multimodal endovascular therapy for acute ischemic stroke. *J Neurointerv Surg* 2013;5:298–301.
22 Vora NA, Gupta R, Thomas AJ, *et al*. Factors predicting hemorrhagic complications after multimodal reperfusion therapy for acute ischemic stroke. *AJNR Am J Neuroradiol* 2007;28:1391–4.
23 Kaur J, Zhao Z, Klein GM, *et al*. The neurotoxicity of tissue plasminogen activator? *J Cereb Blood Flow Metab* 2004;24:945–63.
24 Libman R, Kwiakowski T, Lyden P, *et al*. Asymptomatic hemorrhagic transformation of cerebral infarction does not worsen long-term outcome. *J Stroke Cerebrovasc Dis* 2005;14:50–4.
25 England TJ, Bath PM, Sare GM, *et al*. Asymptomatic hemorrhagic transformation of infarction and its relationship with functional outcome and stroke subtype: assessment from the Tinzaparin in Acute Ischaemic Stroke Trial. *Stroke* 2010;41:2834–9.