MRI-based thrombolytic therapy in patients with acute ischemic stroke presenting with a low NIHSS

Shahram Majidi, MD, Marie Luby, PhD, John K. Lynch, DO, MPH, Amie W. Hsia, MD,
Richard T. Benson, MD, PhD, Chandni P. Kalaria, MD, Zurab Nadareishvili, MD, PhD, Lawrence L. Latour, PhD,
and Richard Leigh, MD

Correspondence
Dr. Leigh
richard.leigh@nih.gov

Abstract

Objective

Treatment of patients with stroke presenting with minor deficits remains controversial, and the recent Potential of rtPA for Ischemic Strokes with Mild Symptoms (PRISMS) trial, which randomized patients to thrombolysis vs aspirin, did not show benefit. We studied the safety and efficacy of thrombolysis in a population of patients with acute stroke presenting with low NIH Stroke Scale (NIHSS) scores screened using MRI.

Methods

The NIH Natural History of Stroke database was reviewed from January 2006 to December 2016 to identify all patients with an initial NIHSS score ≤5 who received thrombolysis within 4.5 hours of symptom onset after being screened with MRI. The 24-hour postthrombolysis MRIs were reviewed for hemorrhagic transformation. Primary outcomes were symptomatic intracranial hemorrhage (sICH) and favorable 90-day outcome modified Rankin Scale score 0–1. Subgroup analysis was performed on patients who would have been eligible for the PRISMS trial, which enrolled patients with a nondisabling neurologic deficit.

Results

A total of 121 patients were included in the study with a median age of 65 and an NIHSS score of 3; 63% were women. The rate of any hemorrhagic transformation was 13%, with 11% of them being limited to petechial hemorrhage. The rate of sICH was <1%. Sixty-six patients had 90-day outcome data; of those, 74% had a favorable outcome. For the subgroup of 81 PRISMS-eligible patients, none experienced sICH. Fifty of these patients had 90-day outcome data; of these, 84% had a favorable outcome.

Conclusions

Thrombolytic therapy was safe in our patients with stroke with minor deficits who were initially evaluated by MRI. Future studies of this population may benefit from MRI selection.

Classification of evidence

This study provides Class IV evidence that for patients with acute ischemic stroke and NIHSS ≤5 screened with MRI, IV tissue plasminogen activator is safe.

Glossary

AHA = American Heart Association; **CI** = confidence interval; **DWI** = diffusion-weighted imaging; **ECASS** = European Cooperative Acute Stroke Study; **FLAIR** = fluid-attenuation inversion recovery; **GRE** = gradient echo; **HCT** = head CT; **HI-1** = hemorrhagic infarction type 1; **HI-2** = hemorrhagic infarction type 2; **HT** = hemorrhagic transformation; **IQR** = interquartile range; **LVO** = large vessel occlusion; **MRA** = magnetic resonance angiography; **mRS** = modified Rankin Scale; **NHS** = NIH Natural History of Stroke; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **PH-2** = parenchymal hematoma type 2; **PRISMS** = Potential of rtPA for Ischemic Strokes with Mild Symptoms; **PWI** = perfusion-weighted imaging; **sICH** = symptomatic intracerebral hemorrhage; **SITS-MOST** = Safe Implementation of Thrombolysis in Stroke–Monitoring Study; **tPA** = tissue plasminogen activator.

Approximately 50% of patients with acute stroke present with a mild deficit (NIH Stroke Scale [NIHSS] score ≤5).[1] Current American Heart Association (AHA)/American Stroke Association guidelines for treatment of acute ischemic stroke state that it is reasonable to consider IV thrombolysis treatment for patients presenting with mild and nondisabling deficits and recommend more studies to identify the risk-to-benefit ratio in this population.[2] However, mild and nondisabling deficits are the most common reason to withhold thrombolysis in emergency departments for patients with acute stroke who are otherwise eligible to receive thrombolytic therapy.[3,4] This is despite multiple studies reporting that approximately 30% of patients who are "too good to treat" have a poor outcome after stroke in the absence of thrombolysis.[4–7] Because a majority of previous thrombolysis trials excluded patients with very mild deficits, the potential benefit of thrombolytic therapy in this population is not fully understood.[8] However, a meta-analysis of the patients included in thrombolytic trials who had a low NIHSS score found them to have a benefit over placebo.[9]

To resolve this issue, the Potential of rtPA for Ischemic Strokes with Mild Symptoms (PRISMS) study was initiated to determine if patients with mild and nondisabling deficits would benefit from IV tissue plasminogen activator (tPA) therapy when comparing with oral aspirin.[8] However, the PRISMS trial was terminated early due to poor enrollment after one third of the planned population had been recruited. The study found that patients in the aspirin group had better functional outcomes and fewer hemorrhagic complications than patients treated with IV tPA. Although the study was underpowered, the results suggested that the practice of thrombolysis in patients with nondisabling stroke may not be warranted.[10]

The PRISMS trial screened patients with head CT (HCT). Although HCT meets the standard of care for screening patients for thrombolysis, MRI can also be used to rapidly screen patients, providing more information while still meeting AHA guidelines.[11,12] In patients with low NIHSS scores for whom the risk/benefit for thrombolysis may be in question, MRI may offer additional information that shifts the balance. For instance, the AHA guidelines recommend against treating patients with >10 cerebral microbleeds on MRI if the potential benefit is unclear.[2] The NIH stroke program has routinely used MRI to screen patients with acute stroke for thrombolysis for more than a decade. The purpose of this study was to investigate the safety and outcome of thrombolysis in patients presenting with NIHSS score ≤5 in an MRI-based practice.

Methods

Magnetic resonance imaging

All patients underwent MRI scanning prior to, and 24 hours after, treatment with IV tPA. The MRI protocol included diffusion-weighted imaging (DWI), gradient echo (GRE) hemosiderin-weighted imaging, fluid-attenuation inversion recovery (FLAIR) imaging, time-of-flight magnetic resonance angiography (MRA), and, in those able to receive gadolinium, perfusion-weighted imaging (PWI). All MRI scans were performed on a 1.5T GE Signa scanner (General Electric Medical Systems, Milwaukee, WI), a 3T Philips Achieva scanner (Philips Healthcare, Best, the Netherlands), or a 3T Siemens Skyra scanner (Siemens AG, Munich, Germany). Scan parameters were similar between scanner types but did evolve over time to maximize diagnostic accuracy.[11]

Population and outcome measures

The study population was derived from patients consented to the NIH Natural History of Stroke (NHS) Study (identification number NCT00009243), an institutional review board–approved observational cohort study of patients with stroke. Study participants were recruited from 2 regional stroke centers (Medstar Washington Hospital, Washington, DC; and Suburban Hospital, Bethesda, MD) affiliated with the NIH Intramural Stroke program.

Stroke patients enrolled in the NIH NHS study from January 2006 to December 2016 were included in the study if they met the following criteria: (1) pretreatment NIHSS score ≤5, (2) screened with MRI, and (3) treated with IV tPA (0.9 mg/kg) within 4.5 hours from symptom onset. Demographic data, stroke risk factors, initial and 24-hour NIHSS score, type of the neurologic deficit (visual, motor, speech, neglect, sensory), vascular territory, and time from symptom onset to IV tPA administration were collected for all patients. Pretreatment MRI scans were reviewed for the following imaging features: the presence of a stroke on DWI, the presence of a perfusion deficit on PWI (when performed), the presence of

a large vessel occlusion (LVO) on MRA, the presence of a likely thrombus on GRE, and the presence of microbleeds, which, when present, were classified as being greater than or less than 10 in number. LVO was defined as a vessel cutoff in the anterior circulation involving the internal carotid artery or the M1 segment of the middle cerebral artery or as a vessel cutoff in the posterior circulation involving the basilar artery or the posterior cerebral artery. If LVO was identified on the pretreatment MRA, the status of its recanalization on the 24-hour MRI was assessed. The presence of a perfusion–diffusion mismatch was assessed visually. The purpose of assessing for a mismatch was to determine the extent of the ischemic event, not to quantify the penumbral salvage, thus quantitative measures were not employed.

The presence of hemorrhagic transformation (HT) on MRI 24 hours post IV tPA was reviewed and graded based on European Cooperative Acute Stroke Study (ECASS) criteria[13] by 2 of the authors (S.M. and M.L.) as hemorrhagic infarction type 1 (HI-1), hemorrhagic infarction type 2 (HI-2), parenchymal hematoma type 1, or parenchymal hematoma type 2 (PH-2); disagreements were adjudicated by a third author (R.L.). Although the ECASS ICH grading criteria were developed based on HCT, in this case they were applied to MRI. Symptomatic intracerebral hemorrhage (sICH) was defined as parenchymal hematoma accompanied by a worsening between the pretreatment and 24-hour post-treatment NIHSS of ≥4 or death. Unlike the ECASS classification of sICH, hemorrhagic infarction was not part of the definition for sICH in this study due to the use of MRI, which has an increased sensitivity for detecting blood products compared with HCT. A favorable outcome was defined by a modified Rankin Scale (mRS) score of 0–1 at 90 days. Discharge disposition post-treatment was also reviewed and dichotomized as discharged to home vs discharged to a facility.

We performed a secondary analysis of our study population to investigate the rate of favorable outcome, hemorrhagic transformation, and sICH among patients who would likely have met inclusion/exclusion criteria for the PRISMS study. We used exclusion criteria similar to the PRISMS study,[8] which excluded patients with any of the following criteria: (1) complete hemianopia (score of ≥2 on NIHSS vision question), (2) severe aphasia (score of ≥2 on NIHSS language question), (3) severe neglect or extinction (score of ≥2 on NIHSS extinction or inattention question), (4) score of ≥2 on the NIHSS motor questions, or (5) functional disability prior to the index stroke (defined as baseline mRS score ≥2).

Statistical analysis
Descriptive statistics were tabulated for the study population and the subset of PRISMS-eligible patients including demographic characteristics, vascular risk factors, admission medications, presenting NIHSS, premorbid mRS, breakdown of the baseline NIHSS components, stroke subtype, timing intervals based on onset to pretreatment MRI and onset to IV tPA treatment, and imaging markers including DWI lesion, PWI deficit, PWI–DWI mismatch, presence of thrombus on

GRE, microbleeds on GRE, and LVO on MRA. The χ^2 test and t test were used as appropriate for continuous and categorical variables. Multiple regression and logistic regression models were performed to identify independent predictors of any HT and favorable outcome using significant variables ($p < 0.10$) from the univariate analysis. There were no missing data for the HT analysis; however, favorable outcome at 90 days was not available for approximately half of the patients. Thus, for the statistical analysis, we used a composite favorable outcome, which was defined as an mRS of 0–1 at 90 days, if available, and when not, as a mRS of 0–1 at 30 days. For patients without mRS data at either of these time points, discharge to home was considered a favorable outcome. Using this composite measure, there were no missing data. SPSS Statistics software v19 (IBM, Armonk, NY) was used for the analysis.

Data availability
Data in this study are monitored by the NIH Office of Human Subjects Research Protections and the Combined NeuroScience Institutional Review Board. Requests for access to the data may be possible if approved by these governing bodies.

Results
During the study period, 1,130 patients were treated with IV tPA at our 2 sites, of whom 245 (22%) had a pretreatment NIHSS ≤5. During this period, 625 of the treated patients were enrolled in the NIH NHS study, of whom 142 (23%) had an NIHSS ≤5. Of the consented patients with NIHSS ≤5, 121 received IV tPA after screening with MRI within 4.5 hours from last seen normal and were included in this study. Twenty-one patients screened with HCT rather than MRI due to contraindications to MRI or lack of scanner availability at the time were not included in the study. The population characteristics for the 121 treated patients are shown in table 1. The median (interquartile range [IQR]) age was 65 (56–77) years, and 63% of the patients were women. The median (IQR) NIHSS score on admission was 3 (2–4) and the median (IQR) time from symptom onset to IV tPA time was 147 (108–188) minutes. Dysarthria (50%) and motor deficit (33%) were the 2 most common presenting symptoms followed by sensory deficit (27%) and aphasia (23%). For 29 patients (24%), the stroke was in vertebrobasilar territory. Diffusion and perfusion lesions were present in 85% and 86% of patients, respectively. Of the 111 patients who had PWI as part of their screening MRI, 72 (65%) patients had perfusion deficit larger than the diffusion lesion based on visual comparison of the PWI and DWI sequences. Thrombus on GRE was evident in 26%, and LVO visualized in 22% of patients. Eighty-one percent (22/27) of the LVO cases also had hyperintense vessels on the baseline precontrast FLAIR. For the 5 cases without visible hyperintense vessels, 3 had LVO in the posterior circulation and 2 had LVO in the anterior circulation. Microbleeds on GRE were present in 28% with no patients having >10. For the 27 patients with LVO, 70% achieved complete recanalization. We did not identify any

Baseline characteristics	N = 121	N = 81 PRISMS eligible
Age, y	65 (56–77)	66 (56–76)
Female	76 (63)	30 (37)
Race		
Caucasian	67 (55)	46 (57)
African American	44 (36)	32 (40)
Hispanic	7 (6)	4 (5)
Others	3 (3)	3 (4)
Systolic blood pressure, mm Hg	155 ± 28	154 ± 28
Serum glucose, mg/dL	121 ± 33	118 ± 36
Hypertension	85 (71)	55 (68)
Diabetes	13 (11)	9 (11)
Hyperlipidemia	59 (50)	35 (43)
Coronary artery disease	14 (12)	7 (9)
Atrial fibrillation	25 (21)	15 (19)
Congestive heart failure	13 (11)	7 (9)
Carotid disease	2 (2)	0 (0)
Previous stroke/TIA	19 (16)	10 (12)
Smoking (current smokers)	20 (17)	16 (20)
Alcohol use	41 (34)	31 (38)
Antithrombotic use	52 (43)	32 (40)
Statin use	42 (35)	28 (35)
Antihypertensive use	64 (79)	41 (51)
Symptom onset to pretreatment MRI, min	103 (73–153)	113 (75–155)
Symptom onset to IV tPA, min	147 (108–188)	158 (110–190)
Premorbid mRS <2	106 (92)	76 (100)
Admission NIHSS	3 (2–4)	3 (1–4)
Neurologic deficit		
Motor	40 (33)	21 (26)
Aphasia	28 (23)	18 (22)
Neglect	15 (12)	12 (15)
Sensory	33 (27)	18 (22)
Dysarthria	60 (50)	39 (48)
Stroke territory		
L MCA/ACA	52 (43)	35 (43)

Table 1 Baseline characteristics of patients with initial NIH Stroke Scale (NIHSS) score ≤5 treated with IV tissue plasminogen activator (tPA) within 4.5 hours vs Potential of rtPA for Ischemic Strokes with Mild Symptoms (PRISMS) eligible patients *(continued)*

Baseline characteristics	N = 121	N = 81 PRISMS eligible
R MCA	40 (33)	30 (37)
Vertebrobasilar	29 (24)	16 (20)
Cardioembolic stroke subtype	46 (38)	30 (37)
Baseline MRI DWI lesion	103 (85)	70 (86)
Baseline MRI PWI deficit[a]	95 (86)	65 (84)
Baseline MRI PWI–DWI mismatch[a]	72 (65)	54 (70)
Thrombus	32 (26)	24 (30)
Large vessel occlusion	27 (22)	17 (21)
Microbleeds ≤10	34 (28)	23 (28)
24-Hour NIHSS	1 (0–2)	1 (0–2)

Abbreviations: ACA = anterior cerebral artery; DWI = diffusion-weighted imaging; MCA = middle cerebral artery; mRS = modified Rankin scale; PWI = perfusion-weighted imaging.
Values reported as median IQR (25–75), n (%), or mean ± SD.
[a] Perfusion study available in 111 patients.

mimics in the population as all patients had imaging confirmation of acute ischemia or stroke, represented as PWI or DWI lesion, respectively.

Hemorrhagic transformation on 24-hour post-treatment MRI was identified in 16 (13%) patients, which consisted of 7 (6%) HI-1, 6 (5%) HI-2, and 3 (2%) PH-2. Symptomatic ICH occurred in only one patient (0.8%) who had a left middle cerebral artery distribution stroke and experienced a PH-2 with an increase in NIHSS from 4 to 13. The patient who had an sICH survived to 90 days, having an mRS of 3 at that time. Outcome mRS was available for 78 patients at 30 days and 66 patients at 90 days. Discharge disposition was available in all 121 patients. The rate of favorable outcome (mRS 0–1) was 77% at 30 days, and 74% at 90 days with 78% discharged to home (table 2 and figure, A). The percentage of patients with a PWI–DWI mismatch was similar between the patients with (70%) and without (69%) a favorable outcome. Comparing stroke location, patients with anterior circulation stroke had a favorable outcome at a rate of 74% compared to the posterior circulation, which had a rate of 83%. Separating patients into those treated within the 3-hour window from those treated in the 3- to 4.5-hour window resulted in 78% vs 75% who had favorable outcomes.

Age ($p < 0.0001$, odds ratio [OR] 0.9, 95% confidence interval [CI] 0.89–0.96), baseline NIHSS ($p = 0.009$, OR 0.6, 95% CI 0.40–0.88), and sex ($p = 0.032$, OR 3.2, 95% CI 1.1–9.5) were independent predictors of favorable outcome. Younger (median of 63 vs 80 years) male (68% vs female 33%) patients

Primary outcome	N (%) (total n = 121)
Hemorrhage	
None	105 (87)
HI-1	7 (6)
HI-2	6 (5)
PH-1	0 (0)
PH-2	3 (2)
Symptomatic ICH	1 (1)
Complete recanalization at 24 hours[a]	19 (70)
Discharge disposition to home	94 (78)
30-Day mRS<2[b]	60 (77)
90-Day mRS<2[c]	49 (74)

Abbreviations: HI-1 = hemorrhagic infarction type 1; HI-2 = hemorrhagic infarction type 2; mRS = modified Rankin scale; PH-1 = parenchymal hematoma type 1; PH-2 = parenchymal hematoma type 2.
[a] Evaluated in 27 patients with large vessel occlusion.
[b] 30-Day mRS available in 78 patients.
[c] 90-Day mRS available for 66 patients.

with less severe baseline NIHSS (median of 3 vs 4) were more likely to have favorable outcomes. There were no independent predictors for incidence of any HT. The multivariate analysis included age, sex, presence of congestive heart failure, baseline NIHSS score, and HT.

Based on inclusion/exclusion criteria, 81/121 patients in our study met the approximated eligibility criteria for the PRISMS trial. The median initial NIHSS score was 3 (IQR 1–4), and there was PWI–DWI mismatch in 54 (71%) of these patients. Ten patients had hemorrhagic transformation (12%); 6 of them were HI-1, 3 were HI-2, and 1 was PH-2. No sICH was seen in this group of patients. The rate of favorable 90-day outcome (mRS score 0–1) was 84% of 50 patients with data available, while 86% of the 81 patients were discharged to home. The figure, B, depicts the distribution of 90-day mRS scores for patients presenting with nondisabling deficits. Favorable 90-day outcome rates were 79% vs 78% in patients with PWI–DWI mismatch vs without mismatch.

Discussion

This study evaluates the safety and efficacy of MRI-guided thrombolysis in a population of patients with acute ischemic stroke who presented with a low NIHSS score, the majority of whom (67%) had a nondisabling deficit. The rate of sICH was exceptionally low in this study and did not occur in patients with a nondisabling deficit. The rate of favorable outcome was in the range of 74%–77% for this study, which is higher than the 69% rate found in the meta-analysis of the thrombolytic trials of patients with NIHSS of 0–4.[9] For the patients with nondisabling deficits in our population, the rate of favorable outcome was 84%, which is higher than either the treatment (78%) or the placebo (81%) arms of the PRISMS trial.[10]

The primary difference between this study and all previous studies looking at thrombolysis of patients with low NIHSS scores is the use of MRI instead of HCT to screen patients prior to treatment. HCT is used to rule out hemorrhagic stroke but rarely contributes to the decision-making process beyond this exclusion. MRI, on the other hand, provides a wealth of information about the brain and the stroke which, particularly in a situation of questionable risk–benefit, may greatly affect the decision-making process. For instance, it has long been the practice of the NIH stroke team to consider >10 microbleeds on GRE to be a relative contraindication to tPA, and, in the case of a nondisabling deficit, would be a sufficient finding for which to withhold thrombolysis. This practice was recently endorsed by the AHA guidelines.[2] Meta-analysis of the sICH for patients with an NIHSS of 0–4 in the thrombolytic trials found a sICH rate of 1.7%[14]; analysis of the Get With The Guidelines–Stroke Registry found an sICH rate of 1.8% for patients with an NIHSS of 0–5.[15] The rate of sICH in our MRI-selected population was 50% less than either of these

Figure Distribution of 90-day modified Rankin Scale (mRS) score

A. Distribution of 90-day mRS score (%)

| 53 | 21 | 9 | 9 | 6 | 1 |
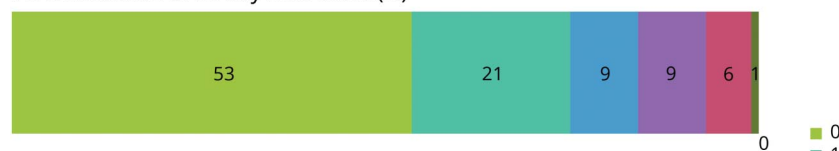
B. Distribution of 90-day mRS among PRISMS-eligible patients (%)

| 62 | 22 | 6 | 4 | 6 | 0 | 0 |

Legend: 0, 1, 2, 3, 4, 5, 6

(A) Distribution of 90-day mRS score among patients with initial NIH Stroke Scale (NIHSS) score ≤5 treated with IV tissue plasminogen activator (tPA) within 4.5 hours from the time of symptom onset. (B) Distribution of 90-day mRS score among patients with NIHSS score ≤5 and nondisabling deficit (similar to Potential of rtPA for Ischemic Strokes with Mild Symptoms [PRISMS] selection criteria) treated with IV tPA.

CT-selected populations and markedly less than the 3.3% rate seen in the PRISMS trial. Although our MRI hemorrhage rate of 0.8% falls on the lower bound of the CI for the rate in the PRISMS trial, when the population is limited to those who would likely be included in the PRISMS trial, the rate of sICH drops to zero. The PRISMS trial also reported the sICH rate based on SITS-MOST criteria,[16] which is more similar to the definition of sICH used in this study, and was found to be 1.3%.

One of the challenges to showing the benefit of thrombolysis in patients with a nondisabling deficit is that the outcome measures used are based on the presence of disability. Thus, in order to demonstrate benefit, either there must be an initially unrecognized deficit (such as difficulty with ambulation),[7] or there must be a worsening of the initial deficit,[6] in which case thrombolysis has the opportunity to exert a benefit on outcome. It is difficult based purely on clinical assessment to determine which patients are at highest risk of worsening. This may be why patients who are "too good to treat" appear to have a 30% chance of a poor outcome. In our study, patients presenting with nondisabling deficits had a 16% chance of poor outcome, possibly reflecting the benefit of tPA. Rapidly improving symptoms in one study of minor stroke were associated with an increased likelihood of subsequent deterioration,[6] while another study did not find any clinical predictors of worsening other than a high NIHSS on presentation.[17] MRI, however, provides several biomarkers that could help assess this risk of deterioration, including thrombus imaging on GRE, vessel cutoff on MRA, hyperintense vessels on FLAIR, and mismatch between DWI and PWI lesions. A prior study looking at MRI predictors of clinical deterioration found that vessel cutoff on MRA and PWI–DWI mismatch were associated with subsequent worsening.[18] In our study, two-thirds of the patients had a PWI–DWI mismatch, and it was even higher in the subgroup with nondisabling deficit, suggesting that such a finding may influence the clinician to treat with thrombolysis despite the otherwise questionable benefit.

Another aspect of MRI-guided treatment that likely influenced this study is the exclusion of stroke mimics. Patients presenting with an MRI that is negative for an ischemic process are generally not treated, and certainly in the situation of a mild deficit, such a patient would not receive thrombolysis. On the one hand, when screening a patient based on HCT, mild deficits may not be convincing enough to conclude that a patient is having a stroke, leading to such a patient going untreated.[19] On the other hand, in everyday practice, stroke mimics are routinely treated with thrombolysis when screened with HCT.[20] The mimic rate in the PRISMS trial was 13%,[10] which was evenly divided between arms, and presumably worked to obscure any potential benefit in the target population. The patients studied in our MRI-screened cohort had confirmation of an ischemic event prior to treatment.

The multivariate analysis did not identify any associations between imaging findings and outcome. This is likely due to the MRIs being the basis for selecting patients in the first place. The association of good functional outcome with lower age and less stroke severity was not surprising; however, the increased benefit for male patients was not expected. Further studies would be needed to determine if this is a meaningful finding.

There are several limitations to this study. Because the use of HCT in screening patients with stroke is rare at our institutions, we are not able to provide a comparison group. Our definition of sICH was different from that of the PRISMS trial, which defined it as "any neurologic decline within 36 hours attributed to ICH by local investigators." [10] Due to the retrospective nature of our study, we could not replicate this definition and instead defined sICH as parenchymal hematoma with neurologic decline ≥4 points on the NIHSS during the first 24 hours. However, the definition of sICH used in this study is similar to that of the SITS-MOST criteria, and was lower in this study compared to when these criteria were applied to the PRISMS trial. The study population is a retrospective assessment of patients prospectively enrolled in an observational cohort study and is subject to sampling bias. The patients were not treated as part of a clinical trial, and thus it is not known if similar outcomes would be achieved in a prospective study. It is not possible in this study to exactly reproduce the selection bias that likely occurred in the PRISMS trial with regards to what constitutes a nondisabling deficit. Only patients enrolled in the NIH NHS study were included in the analysis; however, the rate of low NIHSS in all thrombolysed patients (22%) was similar to that of the patients included in the study (23%), suggesting a representative sample. Patients are generally approached for enrollment in the NHS study immediately after treatment; however, it is possible that a patient approached at a later time point, possibly after a complication occurred, may be less likely to consent, which could artificially inflate the rate of good outcome. However, every attempt is made by the NIH stroke team to consent all treated patients to the NHS regardless of outcome. In addition, missing outcome data could be biased toward patients with a poor outcome. We also do not have data on patients who were not treated based on MRI findings, which would be a useful comparison. Although the use of MRI to select patients for thrombolysis has been standardized at the NIH by a clinical pathway throughout the duration of the study period, practices have changed over time and may vary somewhat between clinicians. Although the results of this study support the practice of MRI-selected treatment of patients with a low NIHSS, considering the above-mentioned limitations, they are not conclusive and should be interpreted as preliminary findings that should be followed up with randomized studies testing this practice. In addition, the practice of screening possible patients with stroke with low NIHSS for treatment will be limited to hospitals with well-established MRI protocols and to patients who are able to safely have an MRI performed.

The use of MRI-guided thrombolysis of patients with a low or nondisabling NIHSS score appears to have been safe and effective at our institutions over the last decade. Future studies investigating the treatment of this population may benefit from MRI-based selection.

Appendix Authors

Author	Location	Role	Contribution
Shahram Majidi, MD	NIH, Bethesda, MD	Author	Designed and conceptualized study, analyzed the data, drafted the manuscript
Marie Luby, PhD	NIH, Bethesda, MD	Author	Interpreted the data, analyzed the data, revised the manuscript for intellectual content
John K. Lynch, DO, MPH	NIH, Bethesda, MD	Author	Major role in acquisition of the data, revised the manuscript for intellectual content
Amie W. Hsia, MD	NIH, Bethesda, MD	Author	Major role in acquisition of the data, revised the manuscript for intellectual content
Richard T. Benson, MD, PhD	NIH, Bethesda, MD	Author	Major role in acquisition of the data, revised the manuscript for intellectual content
Chandni P. Kalaria, MD	NIH, Bethesda, MD	Author	Major role in acquisition of the data, revised the manuscript for intellectual content
Zurab Nadareishvili, MD, PhD	NIH, Bethesda, MD	Author	Major role in acquisition of the data, revised the manuscript for intellectual content
Lawrence L. Latour, PhD	NIH, Bethesda, MD	Author	Interpreted the data, revised the manuscript for intellectual content
Richard Leigh, MD	NIH, Bethesda, MD	Author	Designed and conceptualized study, analyzed the data, finalized the manuscript

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