

Acute Ischemic Stroke Therapy in Infective Endocarditis: Case Series and Systematic Review

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Objectives: To evaluate the safety of acute ischemic stroke (AIS) therapy in patients with infective endocarditis (IE) with intravenous thrombolysis (IVT) or endovascular therapy (EVT) such as mechanical thrombectomy. **Methods:** We conducted a retrospective study of patients who underwent AIS therapy with IVT or EVT at a tertiary referral center from 2013 to 2017, that were later diagnosed with acute IE as the causative mechanism. We then performed a systematic review of reports of acute ischemic reperfusion therapy in IE since 1995 for their success rates in terms of neurological outcome, and mortality, and their risk of hemorrhagic complication. **Results:** In the retrospective portion, 8 participants met criteria, of whom 4 received IVT and 4 received EVT. Through systematic review, 24 publications of 32 participants met criteria. Combined, a total of 40 participants were analyzed: 18 received IVT alone, 1 received combined IVT plus EVT, and 21 received EVT alone. IVT compared to EVT were similar in rates of good neurologic outcomes (58% versus 76%, $P = .22$) and mortality (21% versus 19%, $P = .87$), but had higher post-therapy intracranial hemorrhage (63% versus 18% [$P = .006$]). **Conclusion:** IV thrombolysis has a higher rate of post-therapy intracranial hemorrhage compared to EVT. EVT should be considered as first-line AIS therapy for patients with known, or suspected, IE who present with a large vessel occlusion.

Key Words: Infective endocarditis—ischemic stroke—intravenous thrombolysis—endovascular therapy

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Introduction

Neurological complications are common in patients with infective endocarditis (IE) and incur a worse prognosis.¹ These complications are commonly results of septic thromboembolism to the central nervous system and include ischemic stroke, intracranial hemorrhage (ICH), infectious intracranial aneurysm, meningococcal meningitis,

abscess, and seizure. Of these, ischemic stroke is the most common with an incidence up to 30% in all IE patients,² but the acute management of these patients has not been evaluated in prospective clinical trials.

Treatment with intravenous thrombolysis (IVT) is the standard of care for acute ischemic stroke (AIS) patients presenting within 4.5 hours of symptom onset, however it seems to carry a higher risk of ICH in IE compared to other causes of stroke.³ Endovascular therapy (EVT) using mechanical thrombectomy is now the other standard treatment for AIS in select patients with large vessel occlusion (LVO).⁴

Many patients with AIS due to IE may present with LVO (a quarter present with complete MCA syndrome),⁵ consequently successful recanalization can have implications for long-term neurological outcome and mortality. The purpose of this study was to study the safety and outcomes of IVT and EVT in IE patients presenting with AIS. We hypothesized that the use of EVT incurs lower risk of post-therapy ICH compared to the use of IVT.

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Subjects and Methods

Search Strategy

All procedures used for the systematic review were consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Table 1).⁶ We performed a comprehensive search of MEDLINE (PubMed) and 3 other databases—EMBASE, Web of Science, and Scopus—for subject headings and text of relevant studies from January 1995 (the publication year of successful clinical trial of thrombolysis for AIS) through May 2017. The search strategy for PubMed is available in appendix e-1. References from the included studies were manually reviewed for additional relevant reports.

In accordance with the institutional review board, we performed a retrospective chart review to identify patients at a single tertiary referral center who underwent AIS intervention with IVT or EVT, who were later diagnosed with acute IE (by modified Duke criteria⁷) as the mechanism of stroke during the index admission.

Study Eligibility

Inclusion criteria were applied following the population, intervention, comparator, outcome, and study design approach.⁶ We included studies in any language. Study designs included case reports, case series, case-control studies, and both retrospective and prospective observational studies. Publications were included if they had adequate data reported on (1) an accurate diagnosis of AIS due to IE, (2) the method of AIS therapy, (3) baseline and post-therapy neurological exam in the form of the National Institutes of Health Stroke Scale (NIHSS), (4) post-therapy ICH defined as new intraparenchymal hemorrhage, subarachnoid hemorrhage, subdural hemorrhage, or epidural hemorrhage on a post-therapy CT or MRI scan during the index admission, whether symptomatic or asymptomatic, and (5) neurologic outcomes and mortality post-therapy. Inclusion criteria were similarly applied for the retrospective chart review.

Exclusion criteria were conference abstracts, animal studies, review articles, commentaries, meta-analysis articles, guidelines, articles with insufficient explanation of post therapy ICH or neurologic outcome, and articles with a pediatric population (age < 18 years).

Data Extraction and Management

Two investigators (R.J.M. and S.M.C.) systematically searched the literature and reviewed the identified publications for relevancy based on the above criteria. Full text and charts of included publications were reviewed in detail for data on study design, study population, patient demographics, ischemic stroke mechanism, acute stroke therapy provided, degree of arterial recanalization as defined by the Thrombolysis in Cerebral Ischemia scores,⁸

the presence or absence of post-therapy ICH, symptomatic post-therapy ICH (worsening of the NIHSS by > 3 points, worsening neurological exam due to elevated intracranial pressure, or death directly related to post-therapy ICH during the index admission), dramatic recovery defined as greater than or equal to 10-point reduction in the total NIHSS or a post-therapy NIHSS of 0-1 at 24 hours, neurological outcome, and mortality during the index admission. Good neurological outcome was defined as dramatic recovery following therapy or a modified Rankin scale of disability score of lesser than or equal to 2 by 3 months postdischarge. In addition, we collected demographic data on participants from the retrospective review.

Quality Assessment

The quality of the included studies was assessed using the tool proposed by Murad et al to evaluate case series and case reports.⁹ This tool uses 4 domains for evaluation: selection, ascertainment, causality, and reporting. If a study had adequate data in a domain it was given 1 point. An aggregate score of 4/4 was considered high quality, 3/4 was considered moderate quality, and a score of 2 or less was considered low quality. High and moderate quality studies were deemed to have adequate data to make inferences related to clinical practice. Publication quality was assessed independently by 2 investigators (R.J.M. and S.M.C.). Any disagreements or discrepancies were resolved in consensus with a third investigator (K.U.).

Statistical Analysis

Our main objective was to compare hemorrhagic complications in those participants treated with IVT versus EVT. We hypothesized that hemorrhagic complication rates are higher with IVT, therefore if the participant received both IVT and EVT, they were considered a part of the IVT group. Differences across subgroups were tested with a Fisher's Exact test. A *P* less than .05 expressed differences across subgroups. NCSS 10 statistical software (NCSS, LLC., Kaysville, UT) was used for all analyses.

Results

The systematic search identified 382 publications, and 24 (appendix e-2 for references) met the inclusion criteria (Fig 1) with a total of 32 participants. Agreement was reached to include or exclude all reviewed publications and did not require third party consensus. Of these participants, 14 (44%) received IVT alone, 17 (53%) received EVT alone, and 1 (3%) received combined IVT with EVT and was therefore considered a part of the IVT group. In the retrospective series at our center, an additional 8 participants were identified, of which 4 received IVT alone and 4 received EVT alone (Table 1).

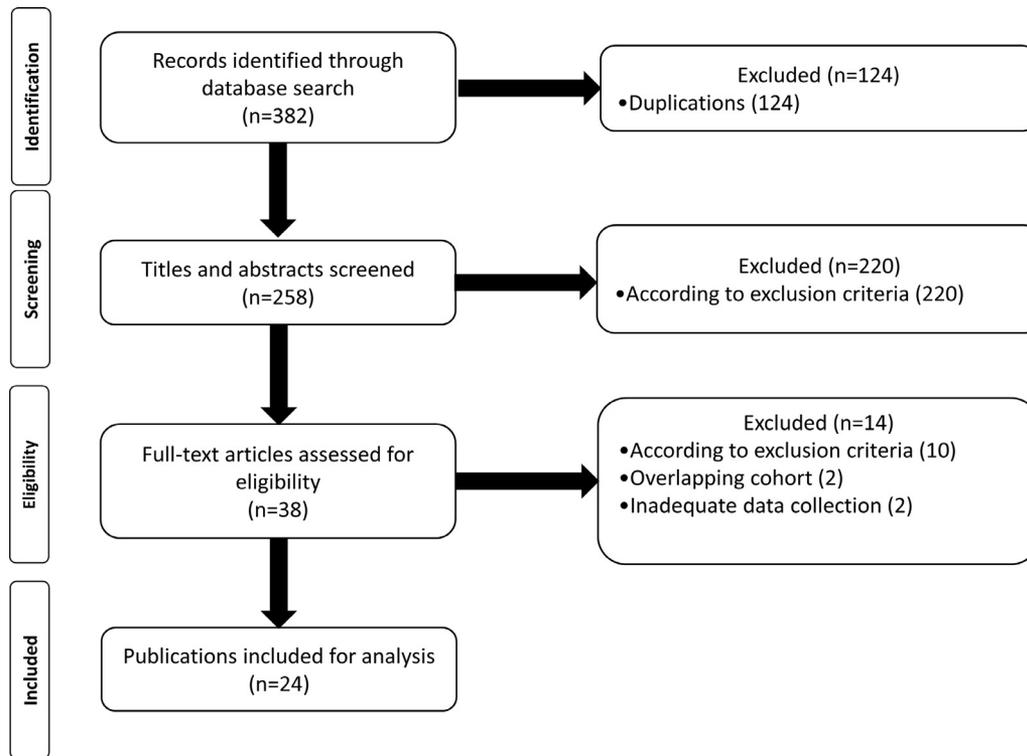


Figure 1. Study flowchart of comprehensive literature search and publication selection.

A total to 40 participants were analyzed, 19 in the IVT group and 21 in the EVT group, with a median initial NIHSS of 13 (interquartile range 10-15) and 14.5 (interquartile range 13-17), respectively ($P = .22$) (Table 2). In the EVT group, 14 (67%) participants underwent mechanical thrombectomy alone and the remaining 7 (33%) had intra-arterial thrombolysis with thrombectomy ($n = 5$) or without thrombectomy ($n = 2$).

Post-therapy imaging was reported in 19 IVT and 17 EVT participants, and any ICH was seen in 12 (63%) and 3 (18%), respectively ($P = .008$). Symptomatic ICH occurred in 8 (42%) IVT and 2 (12%) EVT participants ($P = .07$). Dramatic recovery occurred in 6 (32%) IVT and 11 (58%) EVT participants ($P = .19$). An additional 1 (5%) IVT and 2 (10%) EVT participants achieved a mRS lesser than or equal to 2 by 3 months. Overall good neurological outcome was seen in 7 (37%) IVT compared to 13 (62%) EVT participants ($P = .20$). The in-hospital mortality rate for IVT was 21% compared with 19% for EVT ($P = 1.0$).

Intra-arterial (IA) thrombectomy alone was done in 14 patients and was compared to 7 patients who underwent IA thrombolysis \pm thrombectomy. ICH occurred in 2 (14%) and 1 (14%), respectively ($P = 1.0$). There was 1 (7%) IA thrombectomy in-hospital death, and 3 (43%) with IA thrombolysis \pm thrombectomy ($P = .09$).

The quality assessment for the systematic review of cases involving AIS therapy in IE demonstrated that 16/24 (67%) of included publications were judged to be high quality, 8/24 (33%) were judged to be moderate quality, and no studies were judged to be low quality.

Inadequate reporting of neurologic outcome data was the primary reason reports were downgraded (Supplemental Table 2).

Discussion

The rate of post-therapy ICH in this cohort was higher with IVT compared with EVT in the treatment of AIS in IE. This is consistent with a prior study using administrative data that found higher frequency of ICH diagnosis in AIS with thrombolysis associated with IE diagnosis compared AIS with thrombolysis without IE diagnosis at discharge.³ Compared to this prior administrative data analysis, we are able to report whether ICH was symptomatic and occurred in association with treatment. The rate of symptomatic ICH was higher than what has been reported for all-cause AIS patients treated with IVT (5.9%)¹⁰ and more recent EVT trials (4.4%).¹¹ Our study includes older endovascular methods and devices, and generalizability may be limited. The higher rate of hemorrhagic complications with IE may be related to a different pathophysiologic development between septic thrombus and fibrin/platelet thrombus. The presence of microorganism and inflammatory cells in septic thrombi can allow damage of the endothelium or basement membrane via direct invasion of the arterial wall or through immune-complex deposition, with resulting propensity for hemorrhage.¹²

Up to 48% of IE patients have silent cerebral embolism below the threshold for CT scan detection¹³ and 57% harbor microhemorrhages detected on MRI.¹⁴ These small

Table 1. Clinical characteristics of patients undergoing acute stroke therapy due to infectious endocarditis

Patient	Age/sex	Organism/valve	Site of Occlusion	Treatment modality	Recanalization	Baseline NIHSS	NIHSS at 24 hours and modified Rankin scale at discharge	Post-therapy intracranial hemorrhage
#1	69/Male	<i>Enterococcus faecalis</i> Native AV	No LVO	IV-tPA 77mg	N/A	10	NIHSS 2, mRS 1	No
#2	82/Female	<i>Staphylococcus epidermidis</i> Bioprosthetic AV	No LVO	IV-tPA 70mg	N/A	11	NIHSS 0, mRS 2	Yes Asymptomatic
#3	44/Female	<i>Streptococcus mitis</i> Bioprosthetic AV	Unknown	IV-tPA 90mg	Post-tPA CTA without occlusion.	4	NIHSS 1, mRS 2	Yes Asymptomatic
#4	76/Male	<i>Staphylococcus epidermidis</i> Bioprosthetic AV	Unknown	IV-tPA 61mg	Post-tPA MRA without occlusion.	5	NIHSS 1, mRS 2	No
#5	48/Male	<i>Bartonella quintana</i> Bioprosthetic MV	Left MCA M1	Mechanical thrombectomy – Solitaire and Penumbra	TICI 2A recanalization	12	NIHSS 17, mRS 4	No
#6	77/Male	Unknown Native AV	Left MCA M1	Mechanical thrombectomy – Solitaire and Wingspan stent	TICI 2B recanalization	23	NIHSS 13, mRS 6	Yes Symptomatic
#7	49/Male	<i>Staphylococcus aureus</i> Bioprosthetic AV	Right MCA M1	Mechanical thrombectomy – Solitaire and Penumbra	TICI 3 recanalization	17	NIHSS 17, mRS 6	Yes Symptomatic
#8	56/Male	<i>Streptococcus anginosus</i> Native AV and MV	Right MCA M1	Mechanical thrombectomy – Penumbra with 2mg IA-tPA	TICI 2A recanalization	17	NIHSS 9, mRS 3	No

Abbreviations: AV, aortic valve; CTA, computed tomography angiogram; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; LVO, large vessel occlusion; MCA, middle cerebral artery; MRA, magnetic resonance angiogram; mRS, modified Rankin scale; MV, mitral valve; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Ischemia score.

*Outcome: Reported as post-therapy NIHSS at 24 hours, mRS at time of index hospitalization discharge.

Table 2. Post-therapy intracranial hemorrhage, neurological outcome, and mortality

Type of acute ischemic stroke therapy	IVT	EVT	Overall	P Value
Cohorts and procedural subtypes, n	Twelve cohorts	Sixteen cohorts: Thrombectomy: 12 Thrombolysis: 1 Combined: 3	Thirty-eight cohorts	
Total Participants, n	Nineteen IVT alone: 18 IVT+EVT: 1	Twenty-one Thrombectomy: 14 Thrombolysis: 2 Combined: 5	40	
Age, median (IQR)	61.5 (48-69)	48.5 (37.5-67)	56 (43-69)	0.26
Initial NIHSS, median (IQR)	13 (10-15)	14.5 (13-17)	14 (11-16)	0.22
Post-therapy NIHSS at 24 hours, median (IQR)	4.5 (1-19)	4 (2-10)	4 (1-14)	0.53
Dramatic Recovery at 24 hours	6/19 (32%)	11/19 (58%)	17/38 (45%)	0.19
Number not reporting, n	0	2	2	
Any post-therapy ICH	12/19 (63%)	3/17 (18%)	15/36 (42%)	0.008
Number not reporting, n	0	4	4	
Symptomatic ICH	8/19 (42%)	2/17 (12%)	10/36 (28%)	0.07
Good neurological outcome by 3 months	7/19 (37%)	13/21 (62%)	20/40 (50%)	0.20
In-hospital mortality rate	4/19 (21%)	4/21 (19%)	8/40 (20%)	1.0

Abbreviations: EVT, endovascular therapy; ICH, intracranial hemorrhage; IQR, interquartile range; IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale.

areas of infarction and hemorrhage may increase the risk of thrombolysis. The majority of participants undergoing EVT had mechanical thrombectomy without thrombolysis, thereby limiting the exposure of damaged blood vessels to thrombolytics which can increase symptomatic ICH risk.¹⁵

While IVT is the initial treatment of choice for most AIS patients, our findings warrant caution in patients with known or suspected IE. If EVT is possible, avoiding IVT to perform direct thrombectomy might be considered. Rapid and accurate diagnosis of both AIS and IE are difficult in the rapid thrombolysis treatment process in the emergency department. Clinical suspicion of IE would be important, but techniques to improve the diagnosis of these patients would be beneficial.

The sample size is small, but a strength of this study is the detailed description of participant characteristics and complications. Our study also had limitations. There is a potential reporting bias of case reports and case series. Information on why one treatment option was chosen over another was not readily apparent in many cases, which could influence outcomes. Not all studies reported ICH. NIHSS and ICH were assessed by the treating physicians. Underreporting of ICH complications, in particular in assessments of symptomatic ICH, may have occurred. If all studies that did not report ICH were presumed to have symptomatic ICH complications, the ICH rate would be as high as 33% and symptomatic ICH would be 29%. But there is also a potential to over attribute ICH to therapy, since ICH is common with IE.

Conclusion

Acute reperfusion therapy for AIS in IE appears to accompany high hemorrhagic complication rate. EVT should be considered as first line therapy for AIS due to LVO with known, or suspected IE.

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Statement of Ethics

The study protocol has been approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

R.J.M., S.M.C., A.D., and K.U. contributed to study concept and design. R.J.M., S.M.C., A.D., P.T., D.W., and K.U. contributed to data acquisition and analysis. R.J.M. prepared the first draft of the manuscript. S.M.C., A.D., and K.U. contributed to drafting the manuscript. R.J.M., S.M.C., and K.U. finalized the manuscript.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.04.039.

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