


# Clinical outcomes following reperfusion therapy in acute ischemic stroke patients with infective endocarditis: a systematic review

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## ABSTRACT

**BACKGROUND:** Acute ischemic stroke (AIS) is a common and fatal complication of infective endocarditis (IE); however, there is a lack of understanding regarding treatment efficacy. This systematic review aimed to evaluate the safety and efficacy of intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) in IE patients experiencing AIS.

**OBJECTIVES:** The aim of this study was to perform a systematic review investigating the outcomes of AIS in IE patients receiving IVT and/or EVT as a treatment method and to evaluate the safety and efficacy of these methods of reperfusion therapy.

**DESIGN:** A systematic review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines was conducted.

**DATA SOURCES AND METHODS:** The EMBASE, Cochrane, and PubMed databases were searched for literature published between 2005 and 2021 investigating outcomes of reperfusion therapy post-AIS in IE and non-IE patients. Descriptive statistics were used to describe the overall frequency of clinical outcomes, and groupwise comparisons were performed using Fisher's exact test to assess the significance of groupwise differences.

**RESULTS:** Three studies were finally included in the systematic review. A total of 13.5% of IE patients compared to 37% of non-IE patients achieved a good functional outcome (modified Rankin Scale scores  $\leq 2$ ) ( $P < .001$ ). Furthermore, a larger percentage of the IE cohort achieved good functional outcomes after EVT (22.0%) compared to IVT (10.4%) ( $P = .013$ ). The IE cohort also had a higher 3-month postreperfusion mortality rate (48.8%) compared to the non-IE cohort (24.9%) ( $P < .001$ ). The rate of intracranial hemorrhage (ICH) postreperfusion was also significantly higher in the IE cohort (23.5%) than in the non-IE cohort (6.5%) ( $P < .001$ ).

**CONCLUSION:** AIS patients with IE, treated with IVT, EVT, or a combination of the two, experience worse clinical and safety outcomes than non-IE patients. EVT yielded better functional outcomes, albeit with higher postreperfusion ICH rates, than IVT.

**KEYWORDS:** stroke, cerebrovascular, infective endocarditis, reperfusion, prognosis, pathology, cardiovascular

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**ABBREVIATIONS:** IE, Infective endocarditis; AIS, Acute ischemic stroke; IVT, Intravenous thrombolysis; ICH, Intracranial hemorrhage; EVT, Endovascular thrombectomy; RCT, Randomized Control Trial; mTICI, Modified treatment in cerebral infarction; mRS, Modified Rankin Scale; AF, Atrial fibrillation

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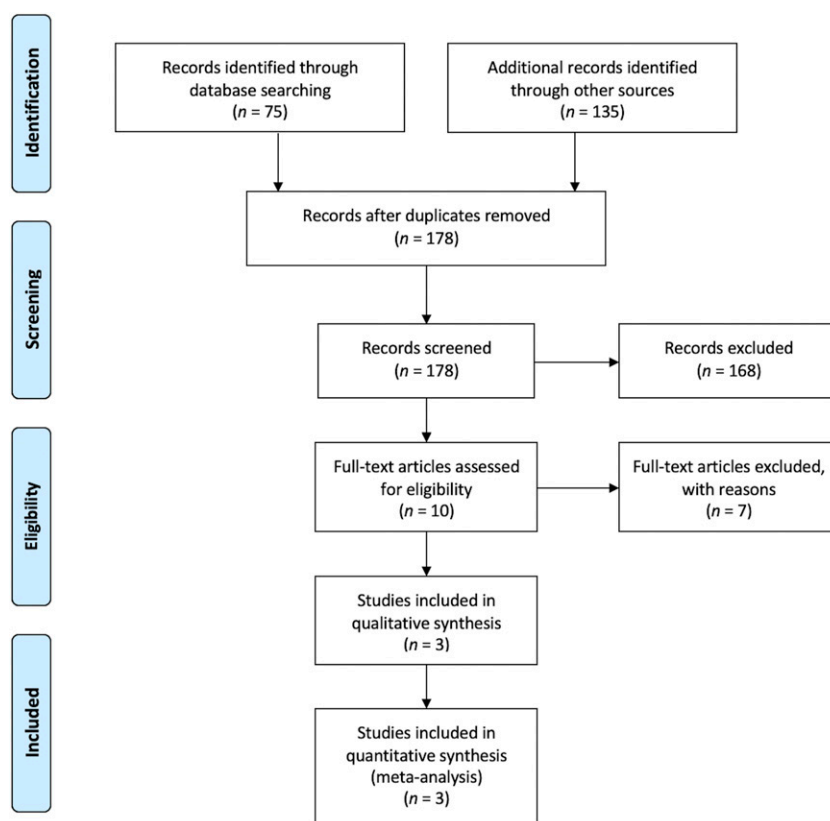
## Introduction

Infective endocarditis (IE) is a well-described cause of cardioembolic acute ischemic stroke (AIS) that presents with various potential complications.<sup>1-3</sup> AIS manifests in up to

40% of IE patients and is associated with a 30% mortality rate.<sup>1,2,4,5</sup> Furthermore, AIS can evolve into cerebral or subarachnoid hemorrhages.<sup>2</sup> The outcomes of AIS secondary to IE display an association with higher rates of cerebral



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**Figure 1.** PRISMA diagram showing the selection strategy for studies included in the systematic review.

complications, such as hemorrhage, meningitis, intracerebral abscess formation, mycotic aneurysms, and recurrent stroke.<sup>4</sup> Neurological complications in the setting of IE occur anywhere in 25–70% of cases; however, AIS is the most common complication, manifesting in up to 40–50% of these patients.<sup>1</sup> The occurrence of AIS in the setting of IE is associated with high morbidity and mortality and thus presents an area of important research.<sup>3,6,7</sup>

AIS treatment guidelines recommend intravenous thrombolysis (IVT) if the presentation is within 4.5 hours of symptom onset. However, in the setting of IE, IVT efficacy is unknown, and it is contraindicated due to the increased risk of intracranial hemorrhage (ICH). Endovascular thrombectomy (EVT) is recommended as a treatment for AIS after IVT for large artery occlusions. In the setting of IE, EVT is associated with a lower risk of ICH than IVT and is thus chosen as a first-line treatment; however, there is insufficient strong clinical evidence in the form of prospective randomized control trials (RCTs) to support widespread recommendations.<sup>8</sup> A recent systematic review reported an increased risk of ICH and worse clinical outcomes in IE patients who received IVT relative to those receiving EVT presenting with AIS.<sup>1</sup> A large retrospective analysis of AIS patients in the setting of IE receiving IVT demonstrated significantly lower rates of favorable outcomes and higher rates of post-IVT ICH than AIS patients without IE.<sup>9</sup> Furthermore, a retrospective case series of 6

patients by Ambrosioni et al investigating EVT as a treatment modality found that no ICH occurred post-EVT, while 4 of the 6 patients experienced dramatic early recovery post-EVT.<sup>10</sup> Overall, the understanding of the best treatment options in AIS patients in the setting of IE is still suboptimal. Therefore, studies aimed at delineating the stroke etiology, acute therapeutic options, biomarkers of prognosis, and poststroke long-term management of IE patients will provide insights to improve clinical outcomes in these high-risk patients.<sup>11–13</sup>

Our understanding of the optimal reperfusion strategy in the setting of IE and AIS remains unclear.<sup>1</sup> Given the increased risks associated with morbidity and mortality in IE patients following AIS, treatment planning continues to pose a clinical challenge.<sup>1,2,4</sup> This systematic review aimed to investigate and evaluate the safety and efficacy of reperfusion therapy (IVT and/or EVT) in the setting of IE and clinical outcomes after reperfusion therapy. A systematic review was chosen to initiate our investigation on this topic, as it enables a detailed overview of available evidence and subsequent identification of areas requiring further research.

## Methodology

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram (Figure 1). Inclusion criteria were established to be prospective or retrospective clinical trials (RCTs, case-controlled or cohort studies) investigating

outcomes of AIS in defined subgroups of IE and non-IE with a minimum sample size of 10. Patients had to have received IVT and/or EVT. Outcomes to be measured included postreperfusion recanalization success, length of hospital stay, and ICH, as well as functional outcome and mortality at 3-months. Successful reperfusion was rated through a modified treatment in cerebral infarction (mTICI) score of 2b-3. Functional outcome was assessed using the modified Rankin Score (mRS) score (mRS 0–2 defined as a good functional outcome) or discharge into home or self-care. Exclusion criteria included a sample size of less than 10 (e.g., case reports), patients under the age of 18, trials presented in abstract form, and/or no related outcome measured.

A literature search for articles published in 2005 or thereafter was conducted in the Embase, Cochrane, and PubMed databases with the keyword search methodology detailed in the Supplementary Information (Search Strategy). As per the PRISMA diagram, the titles and abstracts of the articles obtained from these searches were reviewed to rule out articles that were mismatched to the inclusion criteria (e.g., case reports and review articles). Full-text reading was conducted on the remaining articles to determine whether they should be included in the systematic review as per the inclusion criteria. Articles excluded at this stage included conference abstracts. The remaining articles were included for the quantitative and qualitative systematic review.

Data extraction from the selected clinical trials was conducted using a data extraction sheet to obtain baseline demographics (author, country, and year of publication), study design details (study aims, study type, and inclusion/exclusion criteria), study population characteristics (sample size and type of reperfusion therapy utilized), and outcomes (imaging/clinical parameters used, primary/secondary endpoints, safety outcomes, and the results summary). Methodological quality and bias assessment were performed using the modified Jadad scale (Supplemental Tables 1 and 2). All statistical analyses were performed using STATA (Version 13.0, StataCorp LLC, College Station, Texas, USA). Descriptive statistics will be used to describe the overall proportion/frequency of clinical characteristics and clinical outcomes obtained from individual studies. Groupwise comparisons were performed using Fisher's exact test. The test of difference between means was performed using Hotelling's T-square test. A *P*-value below .05 was considered statistically significant.

## Results

The database yielded 210 relevant results published until May 2021: PubMed (*n* = 75), Embase (*n* = 123), and Cochrane (*n* = 12). After duplicates were removed, 186 articles were identified for review. After the screening of titles and abstracts, 10 articles were selected and were reviewed with a full-text reading. Four of the articles were excluded due to being conference abstracts, 2 studies had fewer than 10 patients receiving IVT and/or EVT, and 1 study did not have a control non-IE subgroup.

In this systematic review, a total of 305 IE patients with a mean age of 60.8 (standard deviation 17.5) presented with AIS, with 207 receiving IVT alone and 67 receiving EVT alone, while 31 received combined treatment. These patients across the 3 studies were compared to 134 236 AIS patients with a mean age of 69.0 (standard deviation 15.0) who did not have IE. In this non-IE cohort, 125875 received IVT alone, 126 received EVT alone, and 8325 received combined treatment. Across two of the studies, 83 IE patients were compared to 188 AF patients as matched case-controls. The non-IE cohort had significantly higher rates of medical comorbidities, with 74.5% (100020/134235) experiencing hypertension compared to 61.0% (186/304) in the IE cohort. Similarly, 22.0% (29552/134234) of the non-IE cohort experienced diabetes compared to 15.1% (46/304) of the IE cohort. All other baseline and procedural characteristics are summarized in Table 1.

Outcomes concerning functional independence after treatment, mortality, ICH/sICH, degree of angiographic reperfusion, rate of recurrent neurological events, and length of hospital stay are summarized in Table 2. The groupwise differences in IE and non-IE cohorts stratified by treatment modality are provided in Table 3. Groupwise comparisons between IE patients receiving IVT or EVT and overall cohorts are also presented in Table 4.

Notably, 1 study had all patients receiving IVT, with some receiving EVT as well. The other 2 studies had all patients receiving EVT, with some patients receiving IVT as well. However, the outcome results in all the included studies were not segregated based on whether the patient received a single mode of therapy or combined therapy. Thus, the results in this study are displayed under subheadings of IVT (with or without EVT) and EVT (with or without IVT).

### *Association with functional outcomes after reperfusion therapy*

Overall, 13.5% (41/304) of patients with IE were significantly lower than 37.0% (49656/134229) of the non-IE patients with AIS who achieved good functional outcome<sup>9,14,15</sup> (*P* < .001).

### *Intravenous thrombolysis*

Data pertaining to functional outcomes after IVT defined on the mRS scale were not available. However, one study reported on the functional outcomes in terms of discharge into home or self-care, indicating that IE patients treated with IVT with or without EVT for an AIS were less likely to achieve good functional outcomes by being discharged into home or self-care than the non-IE AIS cohort (10.4% vs 37.0%; *P* < .001).<sup>9</sup>

### *Endovascular thrombectomy*

AIS patients treated with EVT with or without IVT in the setting of IE were less likely to achieve good functional outcomes (18/82;

**Table 1.** Overall demographics of studies included in the systematic review.

MEDICAL HISTORY	IE (N = 305)	NON-IE (N = 134236)	P-VALUE
Age (years), mean (SD)	60.8 (17.5)	69.0 (15.0)	.500
Female sex, n (%)	135/305 (44.3%)	66300/134236 (49.4%)	.076
Diabetes, n (%) <sup>a</sup>	46/304 (15.1%)	29552/134234 (22.0%)	.003
Hypertension, n (%) <sup>b</sup>	186/304 (61.0%)	100020/134235 (74.5%)	<.001
Hypercholesterolemia, n (%) <sup>c</sup>	35/304 (11.5%)	13475/134234 (10.0%)	.389
Smoker (current or former) <sup>d</sup>	22/80 (27.5%)	54/179 (30.2%)	.768
<i>Procedural information (EVT)<sup>e</sup></i>			
Groin-puncture to reperfusion (mins), mean (SD)	40.7 (33.2)	44.1 (25.5)	.479
Total number of passes, mean (SD)	2.3 (1.9)	2.2 (1.7)	.501
Procedural complications <sup>f</sup>	11/82 (13.4%)	28/186 (15.1%)	.851
<i>Treatment approach (EVT)<sup>g</sup></i>			
Aspiration catheter alone	22/77 (28.6%)	51/175 (29.1%)	1.000
Stent retriever alone	16/77 (20.8%)	65/175 (37.1%)	.013
Combined	35/77 (45.5%)	47/174 (27.0%)	.005
Balloon guide + stent retriever <sup>h</sup>	4/25 (16.0%)	11/79 (14.1%)	.753

Abbreviations: SD = standard deviation; IE = infective endocarditis.

<sup>a</sup>3 missing values (1 from IE cohort and 2 from non-IE cohort) from the Marnat et al study.

<sup>b</sup>2 missing values (1 from IE cohort and 1 from non-IE cohort) from the Marnat et al study.

<sup>c</sup>3 missing values (1 from IE cohort and 2 from non-IE cohort) from the Marnat et al study.

<sup>d</sup>Data only available from 2 studies (Feil et al and Marnat et al) with 12 missing values (3 from IE cohort and 9 from non-IE cohort) from the Marnat et al study.

<sup>e</sup>Data on procedural information was obtained from the 2 studies investigating EVT (Feil et al and Marnat et al).

<sup>f</sup>Procedural complications included device malfunction, dissection/perforation, clot migration/embolization, vasospasm, ICH or other (Feil et al) and dissection, embolization in a new territory and arterial perforation (Marnat et al). There were 3 missing values (1 from IE cohort and 2 from non-IE cohort) from the Marnat et al study.

<sup>g</sup>Data on EVT treatment approach was obtained from the 2 studies investigating EVT (Feil et al and Marnat et al). There were 11 missing values (3 from IE cohort and 8 from non-IE cohort) from the Feil et al study and 9 missing values (3 from IE cohort and 6 from non-IE cohort) from the Marnat et al study.

<sup>h</sup>Balloon guide + Stent retrieval was only performed in the Marnat et al study.

22.0%) than the non-IE (AF) AIS cohort (84/181; 46.4%), which was statistically significant ( $P < .001$ ).<sup>14,15</sup> The rate of good functional outcomes in EVT (22.0%) was significantly higher than that in IVT (10.4%) in the IE cohort ( $P = .013$ ).

#### *Association with mortality after reperfusion therapy*

Overall, only 2 studies provided data on mortality after reperfusion therapy.<sup>14,15</sup> Mortality in the IE cohort occurred due to neurological ( $n = 5$ ), cardiac decompensation ( $n = 1$ ), respiratory failure ( $n = 1$ ), and unknown ( $n=33$ ) causes.<sup>14,15</sup>

#### *Endovascular thrombectomy*

Overall, 48.8% (40/82) of IE patients treated with EVT with or without IVT for an AIS experienced death within 90 days of their treatment, which was significantly higher than the 24.9% (45/181) observed in the non-IE (AF) cohort<sup>14,15</sup> ( $P < .001$ ).

#### *Association with ICH and sICH after reperfusion therapy*

Overall, 23.5% (71/302) of IE patients with an AIS experienced an ICH significantly higher than the 6.5% (8790/134229) observed in the non-IE cohort<sup>9,14,15</sup> ( $P < .001$ ).

#### *Intravenous thrombolysis*

IE patients treated with IVT with or without EVT for an AIS were more likely to experience post-thrombolytic ICH than the non-IE AIS cohort (19.8% vs 6.5%,  $P < .001$ ).<sup>9</sup>

#### *Endovascular thrombectomy*

IE patients treated with EVT with or without IVT for an AIS had a postreperfusion ICH rate of 33.8% (27/80), comparable to the 33.1% (60/181) for the non-IE (AF) cohort ( $P = 1.000$ ).<sup>14,15</sup> However, postreperfusion ICH rates for EVT (33.8%) were significantly greater than those for IVT (19.8%) in IE patients ( $P = .014$ ).

#### *Association with angiographic reperfusion after reperfusion therapy*

Patients with AIS secondary to IE were significantly less likely to achieve successful angiographic reperfusion after EVT with or without IVT than the non-IE (AF) cohort ( $P = .006$ ). Successful reperfusion (mTICI 2b-3) was achieved by the IE cohort 78.3% (65/83) of the time, while the non-IE (AF) cohort achieved it 91.0% (171/188) of the time.<sup>14,15</sup> Furthermore, near-complete reperfusion assessed with a mTICI score of 2c-3 was achieved in 71.4% of cases in the IE cohort

**Table 2.** Clinical outcomes from individual studies included in the systematic review stratified by acute ischemic stroke patients with and without infective endocarditis.

OUTCOME	AUTHORS	DEFINITION	IE		NON-IE		RESULTS
			PATIENTS	TREATMENT	PATIENTS	TREATMENT	
Good functional outcome	Asaithambi et al	Discharge into home or self-care	222	IVT only: n = 207 IVT+EVT: n = 15	134 048	IVT only: n = 125 785 IVT + EVT: n = 8263	Discharge into home/self-care = 49572/134048 (37.0%)
			55	EVT only: n = 47 IVT + EVT: n = 8	104	EVT only: n = 66 IVT + EVT: n = 38	mRS 0-2 = 11/55 (20.0%)
	Mamat et al		28	EVT only: n = 20 IVT + EVT: n = 8	84	EVT only: n=60 IVT + EVT: n=24	mRS 0-2 = 39/77 (50.6%)
<b>Total</b>			305		134236		49656/134229 (37.0%)
Mortality	Feil et al	mRS = 6 at 3-month post-treatment follow-up	55	EVT only: n = 47 IVT + EVT: n = 8	104	EVT only: n = 66 IVT + EVT: n = 38	mRS 6 = 33/55 (60.0%)
			28	EVT only: n = 20 IVT + EVT: n = 8	84	EVT only: n = 60 IVT + EVT: n = 24	mRS 6 = 30/104 (28.8%)
<b>Total</b>			83		188		45/181 (24.9%)
ICH	Asaithambi et al	ICH was defined as per the ICD-9-cm code 430-432	222	IVT only: n = 207 IVT+EVT: n = 15	134 048	IVT only: n = 125 785 IVT + EVT: n = 8263	ICH = 44/222 (19.8%)
			55	EVT only: n = 47 IVT + EVT: n = 8	104	EVT only: n = 66 IVT + EVT: n = 38	ICH = 22/104 (21.2%)
	Mamat et al		28	EVT only: n = 20 IVT + EVT: n = 8	84	EVT only: n = 60 IVT + EVT: n = 24	ICH = 10/25 (40.0%)
<b>Total</b>			305		134236		8790/134229 (6.5%)

(Continued)

Table 2. Continued.

OUTCOME	AUTHORS	DEFINITION	IE		NON-IE		
			PATIENTS	TREATMENT	RESULTS	PATIENTS	TREATMENT
Recurrent stroke occurrence	Feil et al	A recurrent stroke on imaging during the hospital stay	55	EVT only: n = 47 IVT + EVT: n = 8	104	EVT only: n = 66 IVT + EVT: n = 38	Recurrent Stroke = 4/104 (3.8%)
			28	EVT only: n = 8 IVT + EVT: n = 8	84	EVT only: n = 60 IVT + EVT: n = 24	Recurrent Stroke = 0/73 (.0%)
<b>Total</b>			83		188		4/177 (2.3%)
Successful reperfusion outcome	Feil et al	mTICI 2b-3 at the end of the procedure	55	EVT only: n = 47 IVT + EVT: n = 8	104	EVT only: n = 66 IVT + EVT: n = 38	mTICI 2b-3 = 91/104 (87.5%)
			28	EVT only: n = 20 IVT + EVT: n = 8	84	EVT only: n = 60 IVT + EVT: n = 24	mTICI 2b-3 = 80/84 (95.2%) mTICI 2c-3 = 74/84 (88.1%)
<b>Total</b>			83		188		171/188 (91.0%)
Length of hospital stay	Asaithambi et al	Mean number of days (standard deviation) from admission into hospital to discharge from hospital	222	IVT only: n = 207 IVT+EVT: n = 15	134 048	IVT only: n = 125 785 IVT + EVT: n = 8263	Hospital stay days = 7 (8)
			55	EVT only: n = 47 IVT + EVT: n = 8	104	EVT only: n = 66 IVT + EVT: n = 38	Hospital stay days = 11.2 (7.5)
<b>Total</b>			277		134152		7 (8)

Abbreviations: IE = infective endocarditis; IVT = intravenous thrombolysis; EVT = endovascular thrombectomy; mRS = modified Rankin Score; mTICI = modified treatment in cerebral infarction; ICH = intracerebral hemorrhage.

**Table 3.** Comparison between acute ischemic stroke patients treated with intravenous thrombolysis and endovascular thrombectomy stratified by history (or absence) of infective endocarditis.

	IVT			EVT		
	IE	Non-IE	P-value	IE	Non-IE	P-value
Good functional outcome (mRS 0-2)	23/222 (10.4%)	49572/134048 (37.0%)	<.001	18/82 (22.0%)	84/181 (46.4%)	<.001
Mortality (mRS = 6 at 3-months)	-	-	-	40/82 (48.8%)	45/181 (24.9%)	<.001
ICH (post-intervention)	44/222 (19.8%)	8730/134048 (6.5%)	<.001	27/80 (33.8%)	60/181 (33.1%)	1.000
Recurrent stroke (within 3 months)	-	-	-	14/83 (16.9%)	4/177 (2.3%)	<.001
Successful reperfusion (mTICI 2b-3)	-	-	-	65/83 (78.3%)	171/188 (91.0%)	.006

Abbreviations: IE = infective endocarditis; IVT = intravenous thrombolysis; EVT = endovascular thrombectomy; mRS = modified Rankin Score; mTICI = modified treatment in cerebral infarction; ICH = intracerebral hemorrhage.

**Table 4.** Comparison between acute ischemic stroke patients with and without infective endocarditis stratified by reperfusion treatments.

	IE			OVERALL		
	IVT	EVT	P-value	IE	Non-IE	P-value
Good functional outcome (mRS 0-2)	23/222 (10.4%)	18/82 (22.0%)	.013	41/304 (13.5%)	49656/134229 (37.0%)	<.001
Mortality (mRS = 6 at 3-months)	-	40/82 (48.8%)	-	40/82 (48.8%)	45/181 (24.9%)	<.001
ICH (post-intervention)	44/222 (19.8%)	27/80 (33.8%)	.014	71/302 (23.5)	8790/134229 (6.5%)	<.001
Recurrent stroke (within 3 months)	-	14/83 (16.9%)	-	14/83 (16.9%)	4/177 (2.3%)	<.001
Successful reperfusion (mTICI 2b-3)	-	65/83 (78.3%)	-	65/83 (78.3%)	171/188 (91.0%)	.006

Abbreviations: IE = infective endocarditis; IVT = intravenous thrombolysis; EVT = endovascular thrombectomy; mRS = modified Rankin Score; mTICI = modified treatment in cerebral infarction; ICH = intracerebral hemorrhage.

(20/28), while it was achieved in 88.1% (74/84) of cases in the non-IE (AF) cohort<sup>15</sup> ( $P = .070$ ).

#### *Association with recurrent stroke or vascular events after reperfusion therapy*

**Endovascular thrombectomy.** Patients with AIS secondary to IE were significantly more likely to experience a recurrent stroke within 3 months after EVT with or without IVT than the non-IE (AF) cohort ( $P < .001$ ). Recurrent strokes occurred in 16.9% (14/83) of the IE patients, a significantly higher rate than 2.3% (4/177) observed in the non-IE (AF) patients.<sup>14,15</sup>

#### *Association with the length of hospital stay after reperfusion therapy*

Patients with AIS secondary to IE had twice the mean length of hospital stay (14 days) compared to patients with AIS secondary to non-IE causes, who experienced a mean length of hospital stay of 7 days.<sup>9,14</sup>

## Discussion

This systematic review indicates that AIS patients with a history of IE, treated with IVT, EVT, or a combination of the 2,

experience poor functional outcomes in comparison to non-IE patients. Due to a lack of sufficient studies, a meta-analysis could not be performed. However, a primary study investigating functional outcomes in IE after neurological complications found results similar to our study, with less than one-third of their IE cohort achieving a mRS less than or equal to 3 at the 3-month follow-up.<sup>16</sup> IE patients experience a worse safety profile after reperfusion therapy than non-IE patients, experiencing higher rates of mortality, ICH occurrence and recurrent strokes, with previous studies corroborating these poorer outcomes.<sup>17,18</sup> One study had over half of its IE cohort with neurological complications experiencing mortality within 3 months.<sup>16</sup> A retrospective, multi-center analysis of a prospectively collected dataset in Spain found a 45% mortality rate within 1 year in IE patients experiencing AIS.<sup>17</sup>

Regarding treatment methods, IVT should be cautioned in IE due to the significantly higher rate of ICH occurrence compared to the non-IE cohort. A case series of 11 AIS patients receiving IVT found that 4/4 (100%) experienced ICH and/or hemorrhagic transformation.<sup>18</sup> This study found that mortality was experienced by 3/4 (75%) IE patients experiencing AIS and receiving IVT compared to 2/7 (28.6%) IE patients experiencing AIS and not receiving IVT.<sup>18</sup> However, this study has

the limitation of a small sample size, and thus, larger studies evaluating the safety of IVT are necessary.

Second, while EVT achieved better functional outcomes than IVT in the IE cohort, it also had higher rates of ICH occurrence. Notably, all the IVT patients were derived from 1 study, possibly not an accurate reflection of real-world case-mix. Furthermore, the higher rate of ICH occurrence may be due to the lower sample size of EVT patients and with a larger sample size, the rate of ICH occurrence could normalize to a value lower than the rate with IVT. For example, a combined case series and systematic review investigating reperfusion therapy in AIS secondary to IE found a significantly higher rate of ICH occurrence post-IVT (63%) than post-EVT (18%).<sup>19</sup> This study also supported better rates of good 3-month functional outcomes post-EVT (62%) than post-IVT (37%).<sup>19</sup> Furthermore, another systematic review, which included case reports and did not have a control cohort, found no ICH occurrence in 22 patients receiving EVT and a 4.14 times higher likelihood of ICH in IVT patients (18 patients received IVT).<sup>1</sup>

The safety and efficacy of IVT for AIS secondary to IE is not well-established and several previous studies (case reports and case series) report a high-risk of ICH, as mentioned above.<sup>1,18,19</sup> Thus, while AIS is often amenable to IVT, the administration in the setting of IE could lead to devastating outcomes. Although there is not enough research for a uniform recommendation, if a diagnosis or high suspicion index for IE exists, caution with IVT should be exercised.<sup>20</sup> It is important to carefully assess whether IE is suspected to be the causation of AIS in patients presenting within the thrombolytic time window.<sup>19,21</sup> Recent studies have demonstrated the utility of extending brain computed tomography angiography (CTA) to include the heart, which may enable early detection of IE as a causative mechanism of AIS.<sup>22-24</sup>

We postulate that the higher preponderance of ICH in the IE cohort may be due to the underlying disease due to IE. Thus, while AIS is often amenable to IVT, the administration in the setting of IE could lead to devastating outcomes.<sup>1,9,18,19,21</sup> Our study found that successful reperfusion via EVT was achieved in most IE patients. This is a similar finding to a previous systematic review, which found that 18/19 (95%) patients experiencing AIS secondary to IE achieved successful reperfusion post-EVT, and it appeared to be safe as no patients in this study experienced a symptomatic ICH post-EVT.<sup>21</sup> Although EVT seems to have a lower risk of ICH and may be deemed an appropriate medical decision for individual patients, there is not enough clinical evidence available to support generalized recommendations.<sup>1,19</sup> Thus, future studies are required to inform recommendations on the prognostic value, and selection, of appropriate reperfusion therapy for AIS patients with IE.

In terms of baseline risk factors, the non-IE cohort had significantly higher rates of diabetes and hypertension than the IE cohort. This could potentially be since AIS occurrence in the IE cohort is due to the presence of IE and subsequent cardioembolic stroke occurring whereas in the non-IE cohort,

various cardiometabolic risk factors need to be present for an AIS to be likely to occur.<sup>25</sup> This is similarly true for the AF subset of patients, as AF is more likely to develop if the patient has cardiometabolic risk.<sup>26,27</sup>

The non-IE cohort was significantly more likely to receive EVT using the stent retriever approach, whereas the IE cohort was more likely to receive EVT using a combined aspiration catheter and stent retriever. Possibly, the greater complexity of stroke secondary to IE leads to choosing the combined approach more often.<sup>28</sup> However, this still does not enable the same level of reperfusion success as the non-IE cohort (as observed in this systematic review).

The cause of worse AIS outcomes in IE patients has attracted considerable interest in recent literature.<sup>28</sup> Feil et al<sup>14</sup> and Marnat et al<sup>15</sup> retrospective comparative studies both showed that the 24-hour NIHSS change from baseline NIHSS was better in the non-IE cohort than in the IE cohort, illustrating the greater severity of stroke experienced in IE cohorts. Furthermore, the longer hospital stay in the IE cohort in our study also signifies that potentially more severe strokes occurred in this cohort. However, the results pertaining to the length of hospital stay should be approached with caution due to factors such as requiring intravenous antibiotic treatment and potential lack of bed availability.<sup>9</sup> Additionally, other factors, including patient-associated socioeconomic variables and health system parameters, also impact access to acute care services and postreperfusion therapy outcomes in AIS.<sup>29-34</sup>

The infective nature of cardiac vegetation in IE enables septic embolization, which potentially leads to more severe AIS, including multi-territory and/or recurrent stroke and multiorgan complications and worse outcomes.<sup>28</sup> Overall, there have been several case series reports investigating the treatment options for AIS in IE; however, there are no randomized controlled trials (RCTs) comparing IVT and/or EVT to best medical care and a lack of large sample size studies.

This study has demonstrated the higher adverse event rate that occurs in IE cohorts experiencing an AIS compared to a control non-IE stroke population. The risk of embolization is a potentially fatal complication of IE, and its risk is increased in patients with increasing vegetation size, especially in mitral valve and/or staphylococcus IE.<sup>16,35</sup> Clinical outcomes are known to deteriorate after the occurrence of such adverse events; this systematic review indicates the need for early interventions to prevent stroke recurrence.<sup>36</sup> A previous study has found a dramatic reduction in the incidence of stroke from 4.82/1000 patient days in the first week of antibiotic therapy for IE patients to 1.71/1000 patient days in the second week of antibiotic therapy.<sup>37</sup> This decline occurred regardless of the valve or organism involved.<sup>37</sup> Ruttman et al<sup>38</sup> investigated early cardiac surgery in IE and concluded that the risk of secondary cerebral hemorrhage was lower than the potential risk of sepsis, progression of cardiac disease, and recurrent embolism if surgery was delayed.<sup>38</sup>

Limitations of this study include the small number of studies that were included and some studies not segregating patients



receiving either EVT or IVT alone from those patients receiving combined treatment. Furthermore, there were no RCTs, and not all outcomes were present in all the selected studies. The overall quality of the studies was low, as determined by the modified Jadad scale for the comparative studies. Asaithambi et al<sup>9</sup> had a significantly larger sample size in both subgroups than the other 2 studies and caused some overall outcome results to be skewed towards its individual outcome results. Furthermore, it was unknown in most patient cases whether IE was diagnosed before or after the AIS, which would affect management decisions and outcomes. There were no detailed individual patient data on the heart valve lesion size, location, and infecting organism, or the presence of involvement of other body organs, which are important factors contributing to the outcome of AIS and would be valuable clinical factors for predicting prognosis. The scale to assess good functional outcome was varied across the 3 studies, with 1 study reporting it as discharge into home or self-care and the other 2 studies reporting it with mRS less than or equal to 2. However, a previous study reported that discharge into home or self-care as an outcome had a 95% negative predictive value for a mRS score greater than 2<sup>39</sup>. Additionally, some patients included in the study did not have their cause of death specified, which could have been due to something unrelated to the AIS or IE.

This study was unable to explore any clinical or imaging factors that acted as predictors for adverse outcomes or mortality following AIS. Thuny et al<sup>40</sup> found that a low Glasgow Coma Scale score (1.59 times more likely) and having mechanical prosthetic valve endocarditis (15.08 times more likely) were the only predictors of neurological mortality after a first CVC in IE patients.<sup>40</sup> However, there were no other clinical or imaging factors that predicted prognosis in these patients.<sup>40</sup> Thus, future research needs to focus on possible biomarkers or clinical and imaging factors that could predict outcomes in IE patients experiencing AIS.

## Conclusion

In conclusion, AIS occurring in IE patients is an event associated with high morbidity and mortality and is often associated with greater mortality rates, greater rates of adverse events, such as ICH and recurrent neurological events, and lower rates of favorable outcomes than AIS occurring in other populations. Further studies are required to understand the best treatment options and the possible clinical factors that predict prognosis and outcomes in these patients.

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