

**Endovascular treatment for ischemic stroke patients with and without atrial fibrillation, and the effects of adjunctive pharmacotherapy**

*a narrative review*

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*Published in:*  
Expert Opinion on Pharmacotherapy

*DOI (link to publication from Publisher):*  
[10.1080/14656566.2022.2161362](https://doi.org/10.1080/14656566.2022.2161362)

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*Publication date:*  
2023

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

*Citation for published version (APA):*

Alobaida, M., Lip, G. Y. H., Lane, D. A., Sagris, D., Hill, A., & Harrison, S. L. (2023). Endovascular treatment for ischemic stroke patients with and without atrial fibrillation, and the effects of adjunctive pharmacotherapy: a narrative review. *Expert Opinion on Pharmacotherapy*, 24(3), 377-388.  
<https://doi.org/10.1080/14656566.2022.2161362>

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To cite this article: Muath Alobaida, Gregory Y H Lip, Deirdre A Lane, Dimitrios Sagris, Andrew Hill & Stephanie L Harrison (2023) Endovascular treatment for ischemic stroke patients with and without atrial fibrillation, and the effects of adjunctive pharmacotherapy: a narrative review, Expert Opinion on Pharmacotherapy, 24:3, 377-388, DOI: 10.1080/14656566.2022.2161362

To link to this article: <https://doi.org/10.1080/14656566.2022.2161362>



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Published online: 01 Jan 2023.



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REVIEW



## Endovascular treatment for ischemic stroke patients with and without atrial fibrillation, and the effects of adjunctive pharmacotherapy: a narrative review

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### ABSTRACT

**Introduction:** Endovascular thrombectomy (EVT) is associated with good clinical outcomes in patients with ischemic stroke, but the impact of EVT on clinical outcomes in patients with ischemic stroke with and without atrial fibrillation (AF), and the effect of adjunctive pharmacological therapies with EVT, remains unclear.

**Areas covered:** The goal of this narrative review is to provide an overview of studies which have examined: 1) associations between EVT and outcomes for patients following ischemic stroke, 2) associations between EVT and outcomes for patients following ischemic stroke with and without AF, including function, reperfusion, hemorrhage, and mortality, 3) the effect of adjunctive pharmacological therapies peri- and post-thrombectomy, and 4) integration of prehospital care on endovascular treatment outcomes.

**Expert opinion:** There is little evidence from randomized controlled trials on the effect of AF on stroke outcomes following EVT and the safety and efficacy of AF treatment in the peri-EVT such as tirofiban or Intravenous thrombolysis with Non-vitamin K Antagonist Oral Anticoagulant. The available evidence from observational studies on AF and EVT outcomes is inconsistent, but factors such as procedural EVT devices, the center volume, clinician experience, stroke recognition, and inclusion criteria of studies have all been associated with poorer clinical outcomes. Enhancing the clinical network among pre-hospital and hospitals will facilitate direct transfer to EVT centers, reducing stroke onset to EVT time and optimizing stroke outcomes.

### ARTICLE HISTORY

Received 22 April 2022  
Accepted 19 December 2022

### KEYWORDS

Stroke; endovascular thrombectomy; atrial fibrillation; pharmacological; clinical outcomes

## 1. Introduction

Growing evidence has demonstrated the effectiveness of endovascular thrombectomy (EVT) combined with intravenous thrombolysis (IVT) to improve outcomes, such as functional, successful recanalization, and mortality compared to EVT alone in patients with proximal anterior ischemic stroke treated within 6 hours from onset [1,2]. This therapeutic window may be extended in selected patients up to 16 and 24 hours based on the selection criteria of the Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3 (DEFUSE-3) and Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo (DAWN) trials respectively, providing the opportunity to treat stroke patients with wake-up strokes or stroke of unknown time of symptom onset [3,4]. Despite the beneficial effects of IVT and EVT in anterior circulation strokes, two recent high-quality pieces of evidence from randomized clinical trials demonstrated the safety and effectiveness of IVT and EVT in posterior circulation strokes [5,6].

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, associated with a five-fold increase in the risk of ischemic stroke, while AF-related strokes are associated with higher disability and mortality [7–9]. Poorer outcomes with AF-related strokes are often caused by the occlusion of large arteries (i.e. middle cerebral artery) resulting in major ischemic regions, which together with the impaired collateral flow seen in patients with AF may lead to serious disability [10,11]. Which factors may contribute to adverse outcomes in ischemic stroke patients with AF undergoing EVT and whether any adjunctive pharmacological therapy may be beneficial remain less well understood.

The role of intra-arterial adjunctive therapies, such as glycoprotein IIb/IIIa inhibitor, alteplase, urokinase during EVT is controversial, but their use may be beneficial to improve functional outcomes and reduce mortality [12]. There is less evidence from randomized controlled trials and the available data were derived from observational studies in patients following ischemic stroke who underwent EVT [13]. The role of the prehospital care pathway in stroke has improved clinical

**Article highlights**

- Risk stratification of patients in relation to long-term outcomes post-thrombectomy and delays to thrombectomy remain areas of uncertainty.
- Randomised clinical trials examining the efficacy and safety of adjunctive pharmacological therapies are lacking.
- The effect or relevance of atrial fibrillation on EVT outcomes remains unclear as available evidence from observational studies is inconsistent.
- Evidence of intravenous thrombolysis before EVT in patients with atrial fibrillation receiving anticoagulation therapy is unclear
- There is considerable between-centre variation in patient outcomes after EVT for ischaemic stroke.

outcomes, such as functional and mortality following EVT using mobile stroke units.

The goal of this narrative review is to provide an overview of studies which have examined the effect of EVT in ischemic stroke patients with and without atrial fibrillation, including function, reperfusion, hemorrhage, and mortality; the effect of pharmacological therapies peri- and post-thrombectomy; and the integration of pre-hospital care on endovascular treatment outcomes.

### 1.1. Search strategy and selection criteria

PubMed and Google Scholar were searched for articles on EVT for ischemic stroke patients with and without atrial fibrillation and the effects of adjunctive pharmacotherapy, published in the English language from 1988 to 2022. The search strategy used for PubMed database and Google Scholar were different combinations of Medical Subject Headings (MeSH) terms of the National Library of Medicine, which are used to index articles for PubMed and keywords. MESH terms and Keywords were 'Atrial Fibrillation,' 'Ischemic Stroke,' 'Adjunctive Intra-arterial Therapies,' 'Treatment Outcome,' 'Intravenous Thrombolysis,' 'Alteplase,' 'Tenecteplase,' 'Risk Factor,' 'Prehospital Care,' 'Endovascular Treatment' and 'Endovascular Thrombectomy,' or 'Mechanical Thrombectomy.' The selection criteria in the PubMed database and Google Scholar were restricted to observational studies, post-hoc analyses of randomized controlled trials and randomized controlled trials. In addition, from the articles retrieved, additional references were identified by a manual search among the cited references. We used the Scale for the Assessment of Narrative Review Articles (SANRA) to ensure the quality assessment of non-systematic reviews in Appendix.

## 2. Endovascular thrombectomy and intravenous thrombolysis Vs. endovascular alone

The use of IVT in stroke patients within the time window of 4.5 hours has been well established and is considered the main adjunctive therapy for EVT, although there is debate on the necessity of its use in patients arriving directly to stroke centers providing both EVT and IVT, should be treated with IVT. EVT is contraindicated beyond 6–24 hours from stroke onset in patients with large vessel occlusion if not eligible

for DEFUSE-3 or DAWN criteria and those with small vessel occlusions, no vascular access or contraindications to arterial puncture[14]. Similarly, IVT is still not recommended in patients with mild non-disabling, extensive regions of clear hypoattenuation or acute intracerebral hemorrhage (ICH) on computerized tomography (CT) brain imaging or for patients with a history of previous ischemic stroke, severe head injury, or intracranial/intraspinal surgery within 90 days, acute head trauma, history of ICH, subarachnoid hemorrhage, coagulopathy, low-molecular-weight heparin, thrombin inhibitors or factor Xa inhibitors, concomitant Abciximab, concomitant IV aspirin, infective endocarditis, aortic arch dissection or intra-axial intracranial neoplasm[14].

The Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals Multicenter Randomized Clinical Trial (DIRECT-MT) which included 654 patients with anterior ischemic stroke showed that EVT alone was not inferior to IVT plus EVT for favorable functional outcomes (1-point shift in modified Rankin Scale [mRS] at 90 days), with no difference in the rates of reperfusion (OR 0.70, 95% CI 0.47–1.06) and symptomatic intracranial hemorrhage (sICH) (adjusted OR 0.73, 95% CI: 0.47–1.13)[15]. However, liberal margin of non-inferiority, wide confidence intervals, and the delay in randomization with a long door to IVT time may have affected the results. Similarly, the Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands- NO IV (MR CLEAN-NO IV) with 539 ischemic stroke patients, did not identify any significant differences of EVT alone compared with IVT plus EVT for favorable functional outcomes (adjusted OR 0.84, 95% CI 0.62–1.15) as well as the rates of successful reperfusion, sICH and mortality of EVT alone compared with IVT plus EVT (adjOR: 0.73, 95% CI: 0.47–1.13, adjOR: 1.30, 95%CI: 0.60–2.81, adjOR:1.39, 95% CI: 0.84–2.30, respectively)[16]. Subsequently, a meta-analysis of six randomized controlled trials including 2331 patients with acute ischemic stroke which compared EVT alone vs. bridging therapy did not identify difference in good functional outcome (OR: 0.92, 95% CI: 0.80–1.07), sICH (OR: 0.77, 95% CI: 0.52–1.13), and all-cause mortality (OR: 1.06, 95% CI: 0.84–1.35), although there were better recanalization rates in patients treated with bridging therapy (OR: 0.72, 95%CI: 0.57–0.92), while the odds of any intracranial hemorrhage were less in EVT alone group (OR, 0.80, 95% CI, 0.66–0.96)[2]. A meta-analysis of five randomized controlled trials, which evaluated the relationship of time to treatment to EVT outcomes, showed that earlier EVT and IVT treatment (<7.3 hours from stroke onset) was associated with better functional outcomes at 90 days compared to EVT+IVT >7.3 hours[17]. Furthermore, an observational study with a propensity score-matched cohort suggested there was no significant difference between EVT and bridging therapy on the association with physical function at three months for patients following mild ischemic stroke[18]. However, there was a statistically significant difference in stroke onset to thrombolysis or thrombectomy even after matching; this difference can be explained by varying time windows in the performance of IVT and EVT[18]. Although conflicting, the available evidence favors the treatment with bridging therapy in patients with ischemic stroke

( $\leq 4.5$  hrs of stroke onset) who are eligible for both treatments over the EVT alone[2].

Although, alteplase remains the standard-of-care in IVT, tenecteplase may be a safe and effective alternative in patients undergoing both IVT and EVT[13]. One small randomized controlled trial including 202 patients with anterior and basilar ischemic stroke eligible for EVT showed higher recanalization rate, borderline association with better functional outcomes, and similar proportions of sICH in patient treated tenecteplase compared to alteplase[19]. Further, pooled subgroup analysis of two randomized controlled trials demonstrated higher rates of recanalization and functional outcomes in patient treated with tenecteplase compared to alteplase[20]. Accordingly, a meta-analysis of post-hoc pooled subgroup analysis of randomized controlled trials based on non-clinical primary outcomes showed better functional outcomes (modified Rankin Scale; mRS, 0–2) with tenecteplase compared to alteplase (OR: 2.09, 95% CI: 1.16–3.76)[13].

There is still scarce evidence to strongly support the use of tenecteplase over alteplase in EVT eligible patients who are considered to be treated with bridging treatment, but it may be considered as an alternative to alteplase in patients referred for EVT in other centers due to its single-bolus administration[13]. When IVT is the only viable option in patients with acute ischemic stroke, alteplase remains the mainstay of treatment since several studies did not identify a more beneficial effect of tenecteplase over alteplase [13,21–23].

### 3. Factors associated with worse outcomes following endovascular thrombectomy

EVT results in successful recanalization of  $>80\%$  of the large arteries in patients with stroke; however, less than 50% of patients return to complete independence within the following 90 days[24]. Therefore, a successful EVT does not guarantee optimal clinical benefit in half of the patients. It is crucial to identify factors associated with outcomes following EVT in acute ischemic stroke patients to optimize efficacy and safety.

Several observational studies have reported different independent factors associated with worsening functional outcomes at 90 days after EVT in patients following ischemic stroke, including AF, diabetes mellitus, age, prior exposure to anticoagulation, inflammatory parameters, higher baseline NIHSS, general anesthesia, longer time to EVT, and collateral status [25–29]. A recent retrospective study of 417 patients showed that age and higher baseline NIHSS in the hyperacute phase of stroke ( $\leq 6$  hours from stroke onset) are crucial for functional status in both short and long-term follow-up, whereas AF, hyperglycemia, higher baseline NIHSS, and inflammatory state were relevant to the short-term functional status following stroke[30]. First-pass effect and post-interventional reperfusion were important technical parameters to the short-term functional status, while high baseline NIHSS and leukocytosis during the acute phase were associated with high post-procedural ICH[30].

In addition, determinants of long-term outcomes (12 months) in 264 patients with ischemic stroke showed that right hemisphere stroke and NIHSS score at discharge

were predictors of poorer outcome, for delayed functional independence, while successful recanalization may be a positive predictor for good long-term outcomes[31].

Delay in time to treatment was associated with worse functional outcomes after EVT, and functional outcomes can be significantly improved by a shorter time to treatment in anterior or posterior circulation occlusion. Furthermore, time to treatment, collateral status, reperfusion status, the extent of occlusion, and ICH in acute posterior artery occlusion can predict functional outcome and mortality [26,27]. It has been estimated that every 60 minutes delay in stroke onset to EVT results in a lower probability of good functional status ( $-5.3\%$ ) and a higher probability of mortality (2.2%)[26]. Lastly, good collateral status was associated with favorable functional outcomes through a mechanism in which retrograde collateral flow could reach beyond occlusion and provide more access to IVT to the distal territories of the clot and dissolve clot fragments, thereby promoting successful reperfusion[32].

### 4. Atrial fibrillation and endovascular thrombectomy outcomes

To date, the effect or relevance of AF on outcomes following EVT remains undetermined [Table 1]. AF is a common cause of large vessel occlusion that necessitates endovascular treatment [24,33–35]. A subgroup analysis of the MR CLEAN trial of 135 patients with anterior ischemic stroke showed a trend toward a decreased treatment effect of EVT in patients with AF[36]. However, the sample size of AF patients in this study was relatively small and therefore, no definite conclusions could be drawn. Similarly, a meta-analysis of 1351 patients with and without AF showed no difference in the treatment effect size of EVT, functional outcome or sICH in patients with AF compared to those without[37]. A cohort of 1137 patients with and without AF (propensity-score matched) who underwent EVT showed similar rates of any hemorrhagic conversion of ischemic stroke, discharge destination (home or care facility), length of stay or mortality[38]. The Stroke Thrombectomy and Aneurysm Registry (STAR) of  $>4000$  patients who underwent EVT did not find any significant association between AF and EVT outcomes such as ICH or functional status at 90 days, whereas, AF was significantly associated with faster procedural time, fewer passes, and increased first-pass success rates without increased risk of ICH or worse functional outcomes[25]. Consistently, among 417 patients, the presence of AF did not increase the risk of ICH complications after adjustment for age, baseline NIHSS and ASPECT[25]. Several studies have demonstrated that cardioembolic thrombi were more difficult to retrieve using EVT and more EVT passes were needed for successful recanalization compared with non-cardioembolic thrombi [39–41]. It is plausible that the technical ease of recanalization in non-cardioembolic thrombi was related to the shape and feature that has more deformability and less stiffness than cardioembolic thrombi. Conversely, the more abundance of fibrin in the clot provides a stiffer and elastic, presumably decreasing the successful interaction with the EVT device [42,43].



**Table 1.** Summary of studies investigating the effect of endovascular thrombectomy in stroke patients with and without atrial fibrillation.

First Author (Year) (Country)	Ref. (#)	Study type	N Mean (SD) age Median [IQR] n(%) males	Population	Findings
Xiaohua et al. (2016) (China)	[44]	Prospective cohort	35 (10 with AF) AF: 65.00 (8.17) Non-AF: 56.64 (7.93) AF: 4(40%) Non-AF: 21 (84%)	Patients with ischemic stroke who underwent EVT with and without AF	AF group had higher recanalization rates (83% vs 20%) and lower rates of residual stenosis (7% vs 30%), but higher risks for re-bleeding (adjusted for age, sex, weight, blood pressure and underlying diseases) (OR = 1.07 [1.001, 1.148], $p = 0.046$ ; OR = 0.919 [0.853, 0.990], $p = 0.027$ , respectively) No significant difference in stroke severity (NIHSS) and functional independence (mRS) between the groups ( $p > 0.05$ ).
Heshmatollah et al (2017) (Netherlands)	[36]	Retrospective	500 (135 with AF) AF: Median (IQR) 72 (66–80) Non-AF: Median (IQR) 61 (52– 73)	Patient with anterior stroke with and without AF	AF does not modify the effect of EVT ( $p = 0.30$ ). A trend toward a decreased treatment effect of EVT in patients with AF compared to non-AF (cOR 1.0 [0.6–1.9] vs. 1.88 [1.3–2.7], $p = 0.12$ )
Munir et al. (2017) (United states)	[38]	Retrospective PSM	1137 AF: 72 (11) Non-AF: 72 (11) AF: 562 (49.4%) Non-AF: 572 (50.3%)	Patients with acute ischemic stroke who underwent EVT with and without AF	No difference in in-hospital mortality following EVT in patients with and without AF. (20.7% vs 23.9%; $p = 0.07$ ). No difference in rates of hemorrhagic stroke conversion (18.8% vs 20.9%; $p = 0.22$ ), surrogates of disability (17.2% vs 16.9%; $p = 0.97$ )
Churojana et al. (2018) (Thailand)	[49]	Retrospective	134 (50 with AF) AF: 69.2 (12.9) Non-AF: 60.2 (16) AF: 27 (54%) Non-AF: 51 (60.7%)	Patients with anterior and posterior stroke who underwent EVT with and without AF	No significant difference in rate of functional outcome [mRS] (38% vs 38.1%; $p = 0.57$ ), sICH (12% vs 13.1%; $p = 0.85$ ), recanalization (76% vs 76.2%; $p = 0.94$ ) and mortality (20% vs 19%; $p = 0.89$ ) at 90-days in patients with and without AF. No different of EVT outcome between patients with anterior and posterior circulation stroke ( $p = 0.35$ ).
Lin CJ et al. (2020) (China)	[50]	Retrospective	83 (43 with AF) AF: 72.6 (9.5) Non-AF: 70.9 (17.3) AF: 20 (46.5%) Non-AF: 23 (57.5%)	Patients with anterior and posterior ischemic stroke who underwent EVT with and without AF	Significant difference in rates of good functional outcome (mRS) in patients with AF compared to non-AF (55.8% vs 17.5%; $p < 0.01$ ). Non-significant higher rate of substantial reperfusion rate in patients with AF compared to non-AF (72.1% vs 55%, $p = 0.12$ ). Present of AF, Age < 70 years and substantial reperfusion are three predictors of good functional outcomes. (all $p < 0.01$ )
Smaal et al. (2020) (Netherlands)	[37]	Meta- analysis	1351 (447 with AF) AF: 72.8 (10.1) Non-AF: 63.1 (13.7) AF: 229 (51.2%) Non-AF: 480 (53.1%)	Patient with anterior stroke with and without AF	224 (50%) of AF patients were treated with EVT. No difference in functional outcome (mRS) between patients with and without AF. (adjusted OR 1.11 [0.89–1.38], $p = 0.37$ ) AF patients had a lower rate of sICH (adjusted. OR 0.57 [0.30–1.07], $p = 0.08$ ). No significant difference in the treatment effect size of EVT in both groups. (all $p$ value for interaction > 0.05)
Akbik et al. (2021) (United states)	[25]	Retrospective	4196 (1517 with AF) AF: 76 (11) Non-AF: 65.15 (13.7) AF: 640 (42%) Non-AF: 1352 (51%)	Patient with anterior stroke with and without AF	AF is associated with faster procedural time (51 vs 56 minutes, $p = 0.002$ ) and increased rates of first pass success (2% vs 35%, $p = 0.001$ ) without increased risk of ICH in patients treated with EVT (coeffi 0.76 [0.49–1.18], $p = 0.21$ ). Despite decreased procedural times, AF patients have worse functional outcomes (mRS = 3–6) (69% vs 58%, $p = 0.001$ ).

(Continued)

Table 1. (Continued).

First Author (Year) (Country)	(Ref. #)	Study type	N, Mean (SD) age Median [IQR] n(%) males	Population	Findings
Fu et al. (2021) (Australia)	[51]	Retrospective	394 (171 with AF) AF: Median (IQR) 78 (70–83) Non-AF: Median (IQR) 67 (37– 79) AF: 83 (48.5%) Non-AF: 104 (58.4%)	Patients with anterior ischemic stroke who underwent EVT with and without AF	No significant difference in rates good functional outcome (47.4% vs. 48.1%), rates of successful reperfusion (97.4% vs. 99.2%), sICH (2.6% vs. 0.8%) and mortality (21.6% vs. 18%) in patients with and without AF (all $p > 0.05$ ). Improved functional outcome at 90 days in patients with AF and EVT (adjusted. OR 1.98 [1.16–3.38], $p = 0.011$ ). Older age and higher baseline NIHSS were independent predictors of poor functional outcome and higher mortality at 90 days in patient with AF.
Huang et al. (2021) (China)	[45]	Retrospective (PSM)	140 (70 with AF matched) AF: Median (IQR) 68 (62–76) Non-AF: Median (IQR) 69 (62– 76) AF: 36 (51.4%) Non-AF: 36 (51.4%)	Patients with ischemic stroke who underwent EVT with AF	Comparable functional outcome (38.6% vs 44.3%, $p = 0.49$ ) and mortality at 90 days in patient with and without AF (21.4% vs 20%, $p = 0.83$ ). AF was an independent risk factor for any ICH (47.1% vs. 28.6%, $p = 0.02$ ) (OR 1.96; [1.06–3.63], $p = 0.03$ ).
Lasek-Bal et al. (2021) (Poland)	[52]	Retrospective	417 (108 with AF) AF: Median (IQR) 75 (68–81) Non-AF: Median (IQR) 68 (56– 76) AF: 49 (45%) Non-AF: 169 (55%)	Patients with ischemic stroke who underwent EVT with and without AF	No difference in poor functional outcome in patient with AF compared to non-AF at different times (10, 30 and 90 days). (all $p > 0.05$ ) No significant difference in rate of sICH or mortality in patients with and without AF (6.4% vs. 4.8%, $p = 0.73$ ). Prior anticoagulation therapy (VKA vs. NOAC) did not increase the risk of sICH after EVT (12.5% vs 12.8%; FDR-adj. $p = 0.91$ ).
Tong et al. (2021) (China)	[48]	Retrospective (PSM)	1755 (407 with AF matched) AF: Median (IQR) 69 (62–76) Non-AF: Median (IQR) 68 (61– 75) AF: 213 (52.3%) Non-AF: 221 (54.3%)	Patients with acute stroke who underwent EVT with and without AF	No difference in functional outcome (mRS 90-day) (41.3% vs. 40.2%, $p = 0.74$ ), sICH at 24 h (9.4% vs. 9.1%, $p = 0.86$ ), recanalization rates (68.6% vs. 64.9%, $p = 0.27$ ), and mortality 90-day (16.3% vs. 18.4%, $p = 0.44$ ) in Chinese patients with and without AF who underwent EVT.

AF; atrial fibrillation, cOR; common odd ratio, EVT; Endovascular thrombectomy, FDR-adj.; False discovery rate-adjusted, IQR; interquartile range, mRS; Modified Rankin Scale, NIHSS; National Institute of Stroke severity, OR; odds ratio, PSM; propensity score matching, SD; standard deviation, sICH; symptomatic intracranial hemorrhage



Conversely, a post-hoc analysis of a multi-center head-to-head clinical trial suggested that AF was an independent risk factor for any ICH in ischemic stroke patients undergoing stent-retriever thrombectomy, partly attributable to the adjusted anticoagulation status and more retrieval attempts [45]. In general, the increased benefit of EVT outweighed the potential higher risk of ICH in patients receiving anticoagulant treatment [46]. However, a post-hoc analysis of 245 patients with ischemic stroke, indicated that AF was associated with a higher risk of ICH, including those patients with low INR ( $<1.125$ ) [45]. A multicentre observational study which compared the use of vitamin K antagonists (VKA) and non-vitamin-K oral anticoagulants (NOACs) in 1240 patients with AF and stroke found no significant difference in functional outcomes at 90 days; however, the group receiving NOACs tended to have a lower rate of hemorrhagic transformation than the VKA group [47].

Nevertheless, a retrospective study of 417 stroke patient who underwent EVT showed that prior anticoagulant therapy has no potential influence on increasing the risk of intracerebral hemorrhage; the study did not show any relationship between previous anticoagulant therapy and the clinical and non-clinical parameters [30]. A real-world registry study of stroke patients undergoing EVT in China found that patients with AF were more likely to be older and have more severe symptoms on admission, a lower proportion of posterior circulation occlusions, and a shorter time from onset to puncture [48]. After propensity-score matching for baseline characteristics, AF was not independently associated with functional outcomes, recanalization rates, and intra-procedural complications at 90 days. The study concluded there were no differences in the radiological and clinical outcomes following EVT between ischemic stroke patients with and without AF in this Chinese cohort [48]. Similarly, consistent findings in patients with AF and non-AF after propensity score matching showed no significant procedural outcomes (puncture to recanalization, stroke onset to EVT, and reperfusion rate), sICH, a good functional outcome (mRS 0–2) at 90-days and mortality [49].

Propensity matching score may be needed to consider compared to account for differences baseline characteristics and comorbidities. However, some studies did not use propensity matching score but used adjusted models for confounding factors and demonstrated good [50] to neutral effect in functional, procedural, and hemorrhage outcomes and mortality [51–53]. Moreover, a meta-analysis of nine observational studies showed that in patients with AF receiving anticoagulation pre-stroke, both EVT and IVT were not associated with a significant difference in sICH, mortality and recanalization compared to non-anticoagulated patients. However, anticoagulated patients had a relatively lower chance of better functional outcome (mRS of 0–2) at 90 days compared to those who were not anticoagulated (RR: 0.64, 95% CI: 0.50–0.81), but poor functional status in the anticoagulated group may related to the older age, high severe comorbidities and more percentage of cardioembolic stroke. [54] It remains unclear whether patients with AF may benefit more from direct EVT. Thus, based on the available evidence in patient who underwent EVT, AF per se

appears not to be associated with poorer outcomes at 90 days post-EVT.

Lastly, cardiogenic emboli due to non-valvular persistent or permanent AF are associated with a worse prognosis and greater infarction volume than those due to paroxysmal AF. [55] Whether these worse post-stroke outcomes with AF who underwent EVT were related to the AF pattern or type remains uncertain.

## 5. Adjunctive pharmacological therapies to endovascular thrombectomy

Intravenous pharmacological therapies, including fibrinolytic, such as alteplase or tenecteplase, may improve functional outcomes when used as adjunctive therapy to EVT and currently is the only adjunctive therapy suggested by the guidelines [13]. The evidence for the additional use of intra-arterial adjunctive therapy as rescue therapy such as glycoprotein IIb/IIIa inhibitors and intra-arterial alteplase for EVT compared to EVT alone remains unclear [12,14]. Data from the 16 observational studies on the intra-arterial adjunctive medication dosages, route strategies, and medication selection have been inconsistent [12]. There have been no randomized controlled trials on the efficacy of the use of these adjunctive medications, but observational studies have shown the safety and efficacy in improving the reperfusion rate and shorter procedure time with intra-arterial recombinant tissue plasminogen activator (tPA) as rescue therapy [56–58]. A recent meta-analysis of 16 observational studies about intra-arterial medications (glycoprotein IIb/IIIa [tirofiban], urokinase and tPA) with EVT showed no significant difference in successful recanalization, sICH, and mortality between patients receiving EVT with any intra-arterial therapy compared to patients receiving EVT alone (risk ratio [RR]: 1.01, 95%CI: 0.97–1.05, RR: 1.13, 95%CI: 0.87–1.46, and RR: 1.13, 95% C: 0.87–1.46, respectively). However, receiving EVT with any intra-arterial therapy was associated with better functional outcomes at 90 days compared to EVT alone (RR: 1.13, 95% CI: 1.03–1.24). In the subgroup analysis only intra-arterial tPA was associated with better functional outcome (RR: 1.34, 95%CI: 1.03–1.74), while when it was used as a rescue therapy in EVT failure, tPA intra-arterially was associated with good functional outcome and lower mortality (RR: 1.15, 95% CI, 1.04–1.27 and RR: 0.77, 95%CI: 0.65–0.92, respectively) [12]. It is plausible that the effect of these medications on distal territories or small vessels may explain the benefit of better functional outcomes with no difference in successful recanalization [59]. The results should be interpreted with caution given the nature of the design of the available studies, but they can provide an insight for future trials investigating the role of intra-arterial adjunctive medications with EVT, especially when EVT fails to recanalize the occluded artery.

Current guidelines do not suggest the use of any antithrombotic therapy during the first 24 h after IVT due to the increased risk of ICH [13]. Nevertheless, the data on the use of antiplatelet or anticoagulant treatment with EVT are scarce. Tirofiban and Eptifibatide, glycoprotein IIb/IIIa inhibitors that block fibrinogen binding to platelets receptors and eventually prevent platelet aggregation, currently are not suggested in

the treatment of acute ischemic stroke [13,14]. Recently the clinical efficacy and safety of tirofiban in patients with acute ischemic stroke (ESCAPIST), an open-label, randomized controlled trial assessed the efficacy and safety of IV tirofiban in 380 patients with mild to moderate ischemic stroke, who presented within 12 h and were not eligible for either IVT or EVT. In this study tirofiban added to aspirin resulted in better functional outcome at 90 days (mRS 0–2) compared aspirin (79.1% vs. 67.8%, OR: 1.80; 95% CI, 1.12–2.90) without significant increase in sICH[60]. However, when tirofiban was used as an adjunctive therapy to EVT in the Endovascular Treatment With versus Without Tirofiban for Stroke Patients With Large Vessel Occlusion (RESCUE BT) trial, did not show improvement in functional outcomes with a non-significant trend toward intracerebral hemorrhage[61]. The data on other antiplatelet therapy, such as abciximab or aspirin, are based mainly on observational studies with inconclusive results. A subgroup analysis of the Mr CLEAN in patients previously treated with aspirin showed a similar effect size of prior antiplatelet treatment after EVT compared to no antiplatelet treatment (1.7 vs 1.8) with no significant interaction between EVT and prior antiplatelet use. In addition, the absolute risk difference of successful recanalization on functional status was higher with the antiplatelet group compared with the non-antiplatelet group (39% vs 18%)[62]. A recent prospective observational study showed no significant difference in incidence of sICH, or functional status, but more complete recanalization between antiplatelet group compared with no antiplatelet group (77.4% vs 68.2%,  $p = 0.012$ )[63], suggesting that single antiplatelet therapy may serve a useful adjunct in EVT patients who are not submitted to IVT [63]. Interestingly, periprocedural antiplatelet use was not significantly associated with risk of sICH, functional outcome, reperfusion, or mortality after EVT in propensity score-matched [64] and unmatched cohorts. [65]

Although therapeutic dosages of heparin are not indicated in the acute phase of ischemic stroke due to a higher risk of hemorrhagic transformation, periprocedural heparin use has been associated with favorable functional independence [66,67] but with an increased risk of sICH [67,68]. The use of peri-procedural heparin in patients who underwent EVT-only without prior IVT was associated with worse clinical outcomes (neurological at 1 day, 90-days functional, and reperfusion), but with lower rate of ICH[69]. These lower odds of hemorrhagic complications are also observed in similar observational studies with EVT [70,71]. Conversely, although there was substantial variability between 16 centers in periprocedural administration of heparin during EVT, there was no significant difference in functional outcomes, successful recanalization, sICH or mortality. Indeed, centers with more frequent use of heparin had better functional outcomes[72].

EVT appears to be safe in anticoagulated patients with anterior ischemic stroke, but the available evidence on IV-alteplase use in anticoagulated patients (last 48 h) with ischemic stroke was mainly derived from observational studies and remains poor[13]. This uncertainty of evidence may limit the benefit associated with IVT and cause further delay if transferred to a non-thrombectomy capable center.

## 6. Pre-hospital care

The role of the paramedic in pre-hospital stroke care is vitally important for early identification, management, pre-notification, and transfer for fast decision-making. Improvement in paramedic care would allow not only the early administration of IVT in the prehospital setting, but also pre-notification and activation of EVT protocol in a comprehensive stroke center. However, two principles limit the development of a protocol for paramedic triage for a comprehensive stroke center. The first principle is the reduction in stroke cases sent to the primary stroke centers (PSC), while the other is to minimize the overburden with false-positive cases to the comprehensive stroke centers[73].

The Rapid Arterial Occlusion Evaluation Trial (RACECAT) evaluated the outcomes of direct transfer to an EVT center compared to a primary stroke center for thrombolysis followed by transfer to an EVT center. There was no significant difference in functional or mortality outcomes for patients, but the median difference in door-in-door-out times (defined as the duration of time from hospital arrival for IVT to discharge) was relatively quick of 56 minutes[74].

A local protocol or network incorporating paramedics within the stroke care pathway may be useful, given the inconsistent evidence of sensitivity and specificity in clinical diagnostic scales of ischemic stroke in pre-hospital settings [75]. Future development of video triage or ambulance clinical prediction could facilitate EMS assessment and management using Mobile Stroke units (MSU). The evidence of clinical outcomes for IVT using MSU compared with standard of care management varied. A meta-analysis of randomized and non-randomized studies found insufficient evidence with no association between 7- or 90-days mortality and MSU in suspected stroke patients (OR: 1.12, 95% CI: 0.79–1.57)[76]. Moreover, 12 studies (3 randomized and 9 non-randomized) found moderate evidence with improve in functional outcomes with MSU compared with standard of care and higher rate of IVT administration within 60 minutes (OR, 8.24 [95% CI, 3.33–20.44])[76]. There is not enough evidence for the benefit of MSU in EVT [76]. However, MSU seem promising despite the challenges associated with setting up an efficient stroke pathway in different organizations, time variations, dispatcher algorithm of mobile units, and dispatch accuracy limit the reproducibility of results.

## 7. Limitations

The inherent limitations of all narrative reviews can be found in the current review related mainly to its design and methodological quality. The literature was not systematically searched, using a predefined protocol-based search method. Although we pursued to provide insights based on current literature and expert opinion, this may have resulted in unintentional selection bias, lacking the presence of systematic literature approach. Additionally, PRISMA (for data synthesis/extraction) or ROB-tool (risk of bias assessment) were not used in the present narrative review. Although based on its nature, this review was not intended and should not draw definite conclusions, since the majority of the evidence is still scarce

and based on small observational studies, but it may provide some insights to perspectives which may in the future affect the everyday clinical practice.

## 8. Conclusions

There is now growing evidence for the use of EVT in patients with posterior circulation stroke due to LVO. The most common factors associated with worse functional outcomes at 90 days were age, early baseline NIHSS (within 6 hours from stroke onset), AF, diabetes mellitus, prior anticoagulation status higher baseline NIHSS, general anesthesia, longer time to EVT, and collateral status. The effect of AF on EVT outcomes remains undetermined due to inconsistent evidence. Observational studies accounting for potential confounders using propensity score matching suggested no difference between patients with and without AF who underwent EVT. Adjunctive therapy (peri-procedural heparin or antiplatelet use) with EVT has been associated with higher rates of better functional outcomes and lower mortality without increased risk of sICH. Randomized controlled trials are needed to further determine the efficacy and safety of adjunctive pharmacological therapies, such as IVT use with anticoagulated and to determine the effect of AF on EVT outcomes. Evidence showing the efficacy of EVT treatment was acquired mainly in comprehensive stroke centers staffed by fellowship-trained neuro-interventionalists, and evidence showed that high-volume comprehensive centers result in improved clinical outcomes. A networked approach to EVT provision and integration of primary and comprehensive stroke center expertise to develop the EVT pathway in individual regions may enhance the accessibility to EVT.

## 9. Expert opinion

Recent evidence of EVT on stroke outcomes of posterior circulation appears promising. Growing evidence appears to expand the inclusion criteria of EVT treatment in posterior stroke and stroke with prior disability. Stroke treatment and its effects are time-sensitive and any delays in treatment result to worse outcomes. This emphasizes the need for early identification of stroke symptoms with available stroke clinical scales tool in community, pre-hospital personnel, or A&E department. Posterior stroke symptoms appear to be less well recognized compared with anterior stroke symptoms, possibly resulting from the unintended focus of stroke scales that over-emphasize the anterior circulation, such as the middle cerebral artery. Given the lack of validated assessment tools in the pre-hospital phase, especially for the posterior circulation, a necessary paradigm shift in the current prehospital stroke assessment to effectively assess stroke symptoms may help address the imbalance between posterior and anterior stroke recognition and aid in shorter time to recanalization.

The main limitation of endovascular treatment, as with all the current treatment modalities in the hyperacute stroke phase, is that it is time-sensitive and its efficacy is closely correlated with the time it is related. Although EVT provides an additional therapeutic opportunity to thrombolysis in patients with LVO within 4.5 hours from symptom onset and

can also extend the treatment window, still is submitted to several time-related limitations. Even in the hyper-acute phase, the delivery of treatment is limited to thrombectomy-capable centers that are not widely available and not equitable regionally or globally. In other words, geographic accessibility is the factor most likely to affect the equitable provision of EVT. In addition, the time between IVT and EVT varies from minutes to hours, depending on the interfacility transport time, which may affect clinical outcomes. The extended time window of EVT treatment (6–24 hours) benefited patients eligible for the DEFUSE-3 and DAWN trials. However, these trials included selected patients and excluded those with larger infarcts, premorbid disability and M2 occlusions and therefore it is unclear if this time window would be appropriate for patients who did not meet the trial criteria. EVT is further limited by the additional cost, specialized neuro-endovascular expertise required to perform the procedure and service availability 24 hours/7 days. Moreover, treatment affordability has been one of the reasons for the use of lower-dose alteplase in Asia[77], and the requirement for payment before treatment may cause a delay in treatment and effectiveness of therapy.

Variation in recanalization devices, interventionist experience, and high volume of EVT may influence the AF on stroke outcomes and the non-AF on stroke outcomes, especially hemorrhage-related outcomes, which subsequently may affect overall health. The considerable variation between centers in patient outcomes after EVT merits a holistic approach to unify specific approaches, such as a task force or guidelines on specific outcomes measures (time of stroke onset to IVT or EVT).

The time variation was a crucial factor observed in most studies, which was attributed to worse functional status post-stroke. Thus, further studies may shift attention toward approaches that incorporate machine learning or artificial intelligence to improve stroke identification in early stages, which will reduce the variations among centers in the time of stroke onset to IVT or EVT and subsequently improve EVT related-outcomes.

The heterogeneity of findings of endovascular stroke outcomes in patients with and without AF has often been attributed to differences in patient comorbidities, imaging modality and inclusion and exclusion criteria, which have been partially addressed in studies where the cohort was propensity score-matched, which attenuated the between-group effects. Implementing faster treatment requires an efficient system pathway that ensures a continuum of care across pre-hospital to hospital and interfacility transfer [78,79]. Optimizing and streamlining the pathway from pre-hospital (i.e. recognition of stroke, stroke severity and pre-notification of receiving hospital) to in-hospital workflow (i.e. reduce door to CT imaging time, door to thrombolysis or thrombectomy or interfacility transfer to thrombectomy-capable center) will enhance the delivery of care and preserve the salvageable penumbra tissue that is the main goal of the early therapy. A large multi-center clinical trial of 984 patients with severe stroke showed that interfacility transfer was associated with significant treatment delays and a lower chance of good functional independence[80]. There is a need for a stroke

care pathway with an effective workflow of a direct referral to a thrombectomy-capable center with shorter delays in the initial hospital for interfacility transfer. An efficient pathway may help streamline those patients with large vessel occlusion and AF on recent anticoagulation (within 24 hours), in which EVT is the only viable option as IVT is contraindicated. Another system-level factor that could have important implications is the impact of the variability of clinical team levels (senior staff or experienced or less experienced nurses) between the days (weekdays and weekends) or time of the day (office hours or outside office hours) on faster therapies, interfacility referrals and clinical outcomes[81].

Therefore, appropriate expertise and geographical coverage are essential to address the variations and improve the overall clinical outcomes and prognosis. Optimal outcomes in the post-acute phase could be achieved with additional community-based rehabilitation.

Moreover, real-world studies have been suggested to assess the safety and efficacy of certain drugs exerted on such an outcome, which was proved later in randomized control trials. However, its inherited poor design threatens the validity of such findings. The lack of randomized control trials for periprocedural pharmacological treatments (e.g. antiplatelet, heparin, neuro-protective) on stroke outcomes may explain variations between studies outcomes and create more dependence clinical judgment. Theoretically, the pharmacokinetic benefits of tenecteplase as a single-bolus dosage may provide the potential superiority over alteplase and address the time-sensitive obstacle. Faster administration in primary stroke center before further transfer to thrombectomy capable center, and therapy early time to thrombectomy. Thus, it may be plausible that tenecteplase has the potential to be administrated in MSU care; however, this requires further studies to assess the safety and efficacy of bolus-only thrombolytic in prehospital settings.

Further, the ultimate goal is clinical pathway that allows for high-quality communications and referral among different settings, such as comprehensive stroke centers, primary stroke centers and prehospital, facilitating the patient transfer and reducing stroke onset to thrombectomy to optimize stroke outcomes. This can involve multidisciplinary healthcare workers ranging from prehospital staff to specialist centers. Prehospital management can use different prediction models, technologies, or telehealth utilizing the network for rapid identification or activation of receiving hospital, with image sharing system for the better patient pathway.

## Funding

M Alobaida is supported by a scholarship grant from King Saud University for his postgraduate studies (PhD) at University of Liverpool.

## Declaration of interest

- D Sagris has received a research grant from the European Society of Cardiology Council of Stroke. SL Harrison has received grant funding from Bristol Myers Squibb outside of the submitted work. GYH Lip is consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo; no fees are received personally. DA Lane received investigator-initiated educational grants from Bristol-Myers Squibb (BMS), has been a speaker for Bayer, Boehringer Ingelheim, and BMS/Pfizer and has consulted for BMS

and Boehringer Ingelheim. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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