Outcomes in patients with ischaemic stroke undergoing endovascular thrombectomy: Impact of atrial fibrillation

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Objectives: Endovascular thrombectomy (EVT) is associated with good clinical outcomes in ischaemic stroke, but the risk of intracerebral haemorrhage (ICH) and mortality remains common following ischaemic stroke. The effect of concomitant atrial fibrillation (AF) on clinical outcomes following acute ischaemic stroke in patients receiving EVT remains unclear. The aim is to investigate associations between AF and intracerebral haemorrhage and all-cause mortality at 90 days in patients with ischaemic stroke undergoing EVT. *Materials and Methods:* A retrospective cohort was conducted using TriNetX, a global health research network. The network was searched for people aged ≥18 years with ischaemic stroke, EVT and AF recorded in electronic medical records between 01/09/2018 and 01/09/2021. These patients were compared to controls with ischaemic stroke, EVT and no AF. Propensity score matching for age, sex, race, comorbidities, National Institutes of Health Stroke Scale (NIHSS) scores, and prior use of anticoagulation was used to balance the cohorts with and without AF. *Results:* In total 3,106 patients were identified with history of ischaemic stroke treated by EVT. After propensity-score matching, 832 patients (mean age 68 ± 13; 47% female) with ischaemic stroke, EVT and AF, were compared to 832 patients (mean age 67 ± 12; 47% female) with ischaemic stroke, EVT and no history of AF. In the cohort with AF, 11.5% (n = 96) experienced ICH within 90 days following EVT, compared with 12.3% (n = 103) in patients without AF (Odds Ratio (OR) 0.92, 95% confidence interval (CI) 0.68-1.24; p = 0.59). In the patients with AF, mortality within 90 days following EVT was 18.7% (n = 156), compared with 22.5% in patients without AF (n = 187) (OR 0.79, 95% CI 0.63-1.01; p = 0.06). *Conclusion:* In patients with ischaemic stroke undergoing EVT, AF was not significantly associated with intracerebral haemorrhage or all−cause mortality at 90−day follow−up.

Keywords: ischaemic stroke—endovascular thrombectomy—atrial fibrillation—intracerebral haemorrhage—clinical outcomes

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Introduction

People with acute ischaemic stroke and atrial fibrillation (AF) have greater risk of intracerebral haemorrhage (ICH), higher mortality, and comparable response to thrombolysis compared to non-AF patients.[1] These poorer outcomes with AF-related strokes are often caused by the occlusion of large arteries (i.e. middle cerebral artery) resulting in major ischaemic regions, which together with the impaired collateral flow seen in patients with AF, may lead to serious disability and death.[2,3]

Endovascular thrombectomy (EVT) has been shown to improve clinical outcomes such as functional independence, successful reperfusion, ICH, and mortality in patients with ischaemic stroke.[4] Furthermore, the evidence derived from observational studies that investigated the effect of AF on people following an ischaemic stroke who underwent EVT has been inconsistent.[5]

Conflicting results have been reported in previous studies examining associations between AF and outcomes for patients with ischaemic stroke receiving EVT. One large registry study of patients with ischaemic stroke treated by EVT, demonstrated no significant association between AF and functional status, ICH and mortality.[5] However, one post-hoc analysis of multi-centre clinical trial of patients with ischaemic stroke, suggested that AF was associated with a higher risk of ICH at 90 days, even in patients with low INR (<1.13).[6]

Therefore, the aim of this study was to investigate the association between AF and ICH and all-cause mortality at 90 days in patients with ischaemic stroke undergoing EVT.

Materials and methods

A retrospective observation study was conducted with data obtained from TriNetX (https://live.trinetx.com), a global health research network that provides access to electronic medical records retrieved from multiple health care organisations, including specialised medical centres, academic and non-academic medical centres, and community hospitals predominantly in the United States. These data include patient demographics, diagnoses (using International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] codes), medical procedures, medications, and laboratory measurements. This global federated network provides only anonymous data of electronic medical records with no patient identifiable information and identification of participating health care organisations, thus, research studies using this network do not require institutional review boards for ethical approval.

In this analysis, the database was searched for patients recorded on the TriNetX network meeting the following criteria were included: (1) entered on the register prior to March 10, 2022, (2) aged 18 years or above, (3) ischaemic stroke between September 1, 2018 and September 1, 2021, (4) received EVT treatment (extirpation or dilation procedure code), and (5) had an ICD-10 diagnosis code of AF. Patients in the historical control group met the same criteria as the AF group but did not have an ICD-10 diagnostic code for AF. The diagnostic and treatment codes used for the study is available in the **Supplementary Material Table. 1**. 27 of the 58 health care organisations (HCQs) in the TriNetX network within the study time period had patients which met the study inclusion criteria. Given the cohorts were predominantly derived from the United States, the start date of September 1, 2018 was chosen because the American Heart Association/American Stroke Association guideline for early management of patients with acute ischaemic stroke was originally published in January 2018,[7] and the end date September 1, 2021 was chosen to allow for at least 90 days follow-up for all participants. The 90 days outcome assessment has been recommended as the standard for all clinical and pre-clinical studies and trials intending to demonstrate the long-term benefit of acute treatment in stroke.[8]

Statistical analyses

Baseline characteristics were compared using Chi-square $\chi 2$ tests for categorical variables and independent-sample t-tests for continuous variables. Propensity score matching (nearest-neighbour matching with a tolerance level of 0.01 and difference between propensity scores ≤ 0.1) was used to control for differences in the comparison cohorts. A standardised mean difference (SMD) <0.1 were considered well balanced and propensity score density graphs were examined. Using logistic regression, patients with ischaemic stroke who underwent EVT and had AF were 1:1 propensity score matched to patients without AF who had an ischaemic stroke who received EVT, for age, sex, ethnicity, hypertensive diseases, ischaemic heart disease, heart failure, previous transient ischaemic attack, hyperlipidaemia, chronic obstructive pulmonary disease, diabetes mellitus, liver disease, chronic kidney disease, obesity, National Institutes of Health Stroke Scale (NIHSS), intravenous thrombolytics (alteplase) and use of oral anticoagulants. These variables were selected as they may effect on the clinical outcome. Following propensity score matching, logistic regression produced odds ratios (OR) with 95% confidence intervals (CIs) for 90-day incidence of ICH (subcortical, cortical, hemisphere, brain stem, cerebellum, intraventricular, multiple localised) and all-cause mortality, comparing stroke patients with AF who underwent EVT with propensity matched controls (without AF). Kaplan-Meier survival curves for all-cause mortality at 90-days from the date of the index stroke by AF status were used. Statistical significance was set at $p < 0.05$.

Results

Within the TriNetX network at the time of the analysis, there were 1718 patients with ischaemic stroke who underwent EVT and had AF, and 1388 patients with

ischaemic stroke who underwent EVT who did not have AF between September 2018 and September 2021 (shown in Fig. 1). Patients with ischaemic stroke who underwent EVT who had AF were significantly older than those with ischaemic stroke and EVT who did not have AF (mean ± SD: 73.6 ± 12.6 vs. 61.1 ± 14.8, $p < 0.0001$). The patients with AF had a higher prevalence of white patients (77.8 vs. 67.1%, $p < 0.0001$) and a lower prevalence of black or African American patients (13.9 vs. 22.7%, $p < 0.0001$). Patients with ischaemic stroke, EVT and AF had a significantly higher prevalence of history of diabetes mellitus, hypertension, transient ischaemic attack, ischaemic heart disease, heart failure, chronic kidney disease, hyperlipidaemia, chronic obstructive pulmonary disease, obesity and intravenous thrombolysis (shown in Table. 1) than those without AF who experienced an ischaemic stroke and received EVT.

After 1:1 propensity score matching, there were 832 patients with AF and 832 patients without AF, and the cohorts were well balanced on all included characteristics (all $p > 0.05$ and SMDs< 0.1, except for the INR level) (shown in Table. 1). After propensity score matching, Kaplan-Meier survival analysis showed the odds of 90-day ICH were not significantly different for patients with ischaemic stroke who underwent EVT and had AF compared to the propensity score-matched non-AF patients (OR: 0.92 [95% CI 0.68-1.24]; survival probability of ICH within 90-day: 87.1 vs. 85.9%, log-rank test $p = 0.54$, shown in Fig. 2).

After propensity score matching, Kaplan-Meier survival analysis showed odds of 90-day all-cause mortality were lower for AF patients with ischaemic stroke undergoing EVT compared to the propensity score-matched non-AF patients, but this was not statistically different (OR: 0.79 [95% CI 0.63-1.01]; survival probability of all-cause mortality within 90-day: 79.4 vs. 75.8%, log-rank test $p = 0.049$, shown in Fig. 3).

Discussion

In the present study of over 1,650 patients with ischaemic stroke treated by EVT in multiple HCOs, AF patients with ischaemic stroke treated by EVT were not significantly associated with greater ICH or all−cause mortality at 90−days than non-AF patients with ischaemic stroke treated by EVT, when propensity score matched for age, sex, race, and NIHSS, prior anticoagulation status and several comorbidities.

AF is one of the leading causes of large vessel occlusion that mandates EVT treatment. A subgroup analysis of the MR CLEAN trial of 135 patients treated by EVT with and without AF demonstrated no significant difference in the effect of EVT treatment in patients with and without AF, despite a non-significant trend towards a decreased treatment effect in AF patients.[9] Similarly, a meta-analysis of 1351 patients with and without AF also showed no difference in the treatment effect size of EVT, functional outcome or symptomatic ICH in patients with AF compared to those without AF.[10]

Indeed, it has been debated whether AF per se increases the risk of ICH or mortality for ischaemic stroke patients undergoing EVT. A post-hoc analysis of multi-centre clinical trials of 140 patients with ischaemic stroke showed that AF was an independent risk factor for any ICH in patients with ischaemic stroke treated by EVT, even in patients with low INR (<1.13).[6] However, there are other studies which indicate that EVT is safe and has no influence on anticoagulated patients.[11-13] These studies were

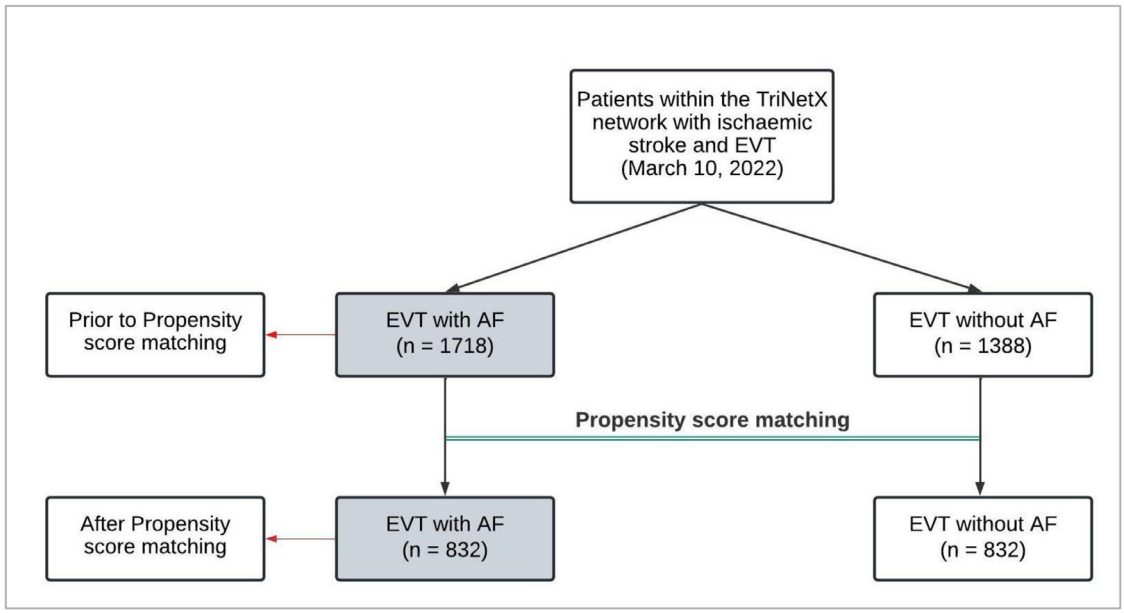

Fig. 1. *Flow diagram of selected patients with ischaemic stroke cohort. AF: Atrial fibrillation, EVT: Endovascular thrombectomy.*

Table. 1. *Baseline characteristics for patients who underwent endovascular thrombectomy and atrial fibrillation and controls who underwent endovascular thrombectomy without atrial fibrillation before and after propensity score matchings.*

% (N)	Initial population			Propensity score-matched populations			
	EVT and AF (n = 1,718)	EVT and no AF (n = 1,388)	p value	EVT and AF (n = 832)	EVT and no AF (n = 832)	p value	SMD
Demographics							
Age, years, mean ± SD	73.6± 12.6	61.1 ± 14.8	<0.0001	68 ± 13.2	67.7 ± 11.9	0.70	0.02
Female	52.8 (908)	42.8 (595)	<0.0001	45.9 (382)	47.2 (393)	0.58	0.006
Race							
White	77.8 (1,336)	67.1 (932)	<0.0001	71.1 (592)	71.7 (597)	0.78	0.01
Black or African American	13.9 (239)	22.7 (316)	<0.0001	18.8 (157)	18.6 (155)	0.90	0.006
Asian	1.16 (20)	1.08 (15)	0.83	1.2 (10)	1.2 (10)	1	0
American Indian or Alaska Native	0.58 (10)	0.72 (10)	0.63	1.2 (10)	1.2 (10)	1	0
Native Hawaiian or Other Pacific Islander	0.58 (10)	0.72 (10)	0.63	0	0	-	-
Unknown race	6.9 (119)	8.4 (117)	0.11	8.4 (70)	8.4 (70)	1	0
Comorbidities							
Hypertensive diseases	80.2 (1,378)	73.4 (1,020)	<0.0001	76.4 (636)	77.7 (647)	0.52	0.03
Diabetes mellitus	32.5 (558)	27.8 (387)	0.005	30.2 (251)	31.2 (266)	0.43	0.04
Previous TIA	15.4 (266)	2.7 (38)	<0.0001	3.8 (32)	4.4 (37)	0.53	0.03
Hyperlipidaemia	53.9 (927)	44.8 (623)	<0.0001	49.5 (412)	51.1 (425)	0.52	0.03
Chronic ischaemic heart disease	31.5 (542)	23.6 (328)	<0.0001	29.6 (247)	29.1 (242)	0.78	0.01
Heart failure	39.5 (679)	16.3 (227)	<0.0001	24.3 (202)	23.6 (197)	0.77	0.01
Chronic obstructive pulmonary disease	13.8 (238)	9.7 (135)	0.0004	12.5 (104)	12.3 (102)	0.88	0.007
Liver disease	3.4 (58)	2.6 (36)	0.20	3.7 (31)	3.4 (28)	0.69	0.02
Chronic kidney disease	17.7 (305)	11.1 (154)	<0.0001	13.4 (112)	15 (125)	0.36	0.04
Overweight and obesity	19.5 (335)	15.7 (218)	0.006	15.2 (127)	17.4 (145)	0.23	0.05
Intravenous thrombolysis	31.9 (549)	24.5 (340)	<0.0001	24.3 (202)	25.1 (209)	0.69	0.02
INR	1.36 ± 1.6	1.14 ± 0.7	<0.0001	1.36 ± 1.8	1.16 ± 0.9	0.01	0.13
Stroke severity (NIHSS)							
NIHSS score 0-9	22.2 (383)	26.1 (362)	0.01	22.4 (187)	24 (200)	0.45	0.03
NIHSS score 10-19	38.1 (656)	42.8 (595)	0.008	40 (333)	39 (325)	0.68	0.02
NIHSS score 20-29	26.8 (461)	23.3 (324)	0.02	25.7 (214)	26 (217)	0.86	0.008
NIHSS score 30-39	2.3 (40)	2.6 (37)	0.54	2.5 (21)	2.16 (18)	0.62	0.02
NIHSS score 40-42	0	0.7 (10)	0.0004	0	0	-	-

INR: international normalized ratio, NIHSS: National Institutes of Health Stroke Scale, SD: standard deviation, SMD: standardized mean difference, TIA: transient ischaemic attack (without residual deficits).

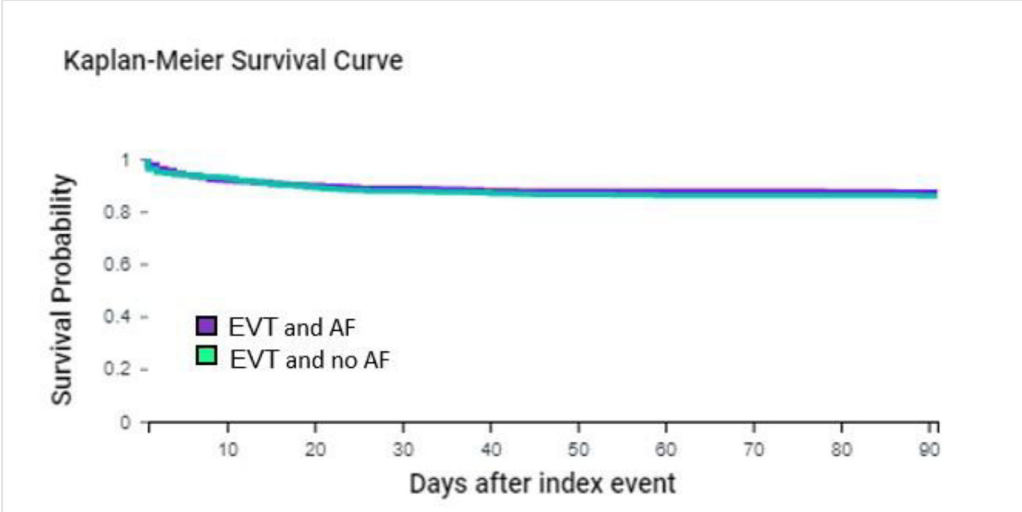

Fig. 2. *Kaplan-Meier curve depicting the risk of intracerebral haemorrhage events within 90 days after endovascular thrombectomy (EVT) in patients with ischaemic stroke, with and without atrial fibrillation.*

small in sample size and outcome events, so these findings must be confirmed in larger cohorts.

In contrast, previous retrospective observational studies using multivariate adjusted models demonstrated no significant difference in ICH (at 1-day and 90 days), mortality or functional status at 90 days.[5,14-16] Similar to the present study, two previous retrospective observational studies in the United States (n = 562 AF vs 572 non-AF) and China (n = 407) used 1:1 propensity score matching in patients with and without AF demonstrated no significant difference in ICH (at 1-day and 90 days), mortality or good functional status at 90 days.[17,18] The present analyses further supports evidence from previous observational studies showing that presence of AF did not impact on the rate of ICH or all-cause mortality within 90 days of follow-up in patients with ischaemic stroke who underwent EVT, when compared to ischaemic stroke patients without AF.

Limitations

This study has several limitations. The ICD codes derived from the electronic medical records are limited and may differ among HCOs,[19] and the impact of attending different HCOs cannot be determined due to data privacy. It is worth noting that there is a possibility of covert AF in the control group that was diagnosed later but not reported or never diagnosed, which could impact the outcome. Similarly, in the AF group, two possible causes of stroke could be due to AF or other atherosclerotic artery occlusions. The detailed cause of death, such as cardiovascular or cerebrovascular mortality, was not available, and

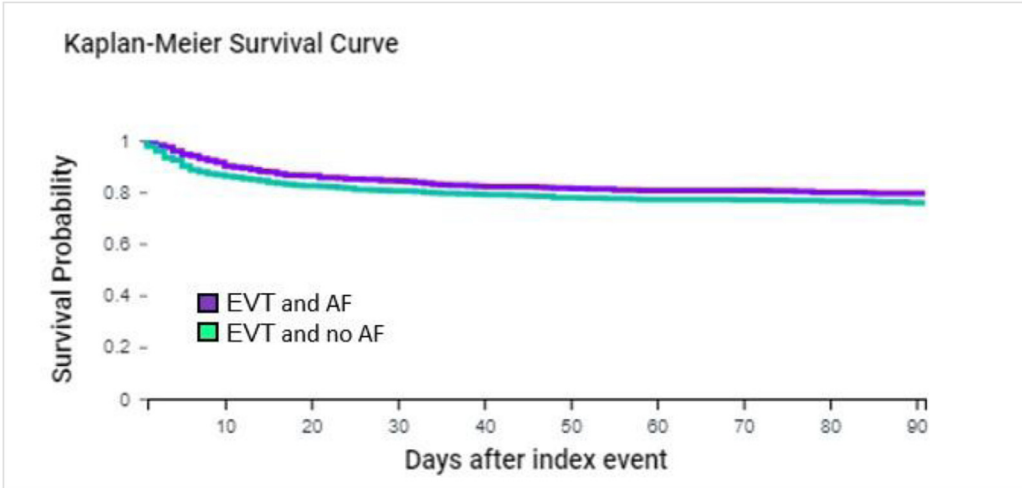

Fig. 3. *Kaplan-Meier curve depicting the risk of all-cause mortality within 90 days after endovascular thrombectomy (EVT) in patients with ischaemic stroke, with and without atrial fibrillation.*

reported mortality is 'all-cause mortality', and deaths occurring outside the TriNetX network will not be captured. Although this was a multi-HCO, incorporating more than 50 centres, data may not be representative of the broader population of the US. The propensity score was matched for factors such as age, sex, co-morbidities, stroke severity, IVT, and prior anticoagulation status. However, residual confounding may be present as some variables of interest were not available, such as treatment time to therapy (features of treatment time, such as stroke onset to IVT, time to deployment, time to reperfusion, time door in to door out), degree of reperfusion, rate of good reperfusion, and pre-stroke disability (modified Rankin Scale 2-6). Stroke severity score (NIHSS) for assessment of pre-stroke and post EVT functional status was also not available. In addition, details regarding oral anticoagulation, such as timing of oral anticoagulation re-initiation post stroke, were not available. Further, a previous study has reported surrogate measures for functional status (modified Rankin Scale), such as discharge destination (home, relative's or friend's home, rehabilitation facility, and nursing home) at 90 days in the poststroke cohort,[20] but this surrogate marker was not clearly defined in this network.

Conclusion

In patients with ischaemic stroke undergoing EVT, AF was not significantly associated with increased risk of intracerebral haemorrhage or all−cause mortality at 90−day follow−up. This study adds support to the existing evidence that AF does not significantly affect outcomes for patients undergoing EVT. Further research may examine different EVT devices on ICH and mortality for patients with ischaemic stroke and AF and whether type of AF plays a role in clinical outcomes following EVT.

Statement of Ethics

Ethical approval for this study was waived by TriNetX. Research studies using the TriNetX federated network do not require ethical approval or patient informed consent as no patient identifiable information is received.

Data availability statement

The data underlying this article are available in the TriNetX research network at https://live.trinetx.com with a request for access to the TriNetX network, but costs may be incurred.

Declaration of Competing Interest

MA and AH: report there is no competing interests to declare.

SLH: received grant funding from Bristol Myers Squibb outside of the submitted work.

DAL: 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.

PU: is an employee of TriNetX LLC.

GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2022.106917.

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