








Differential effect of mechanical thrombectomy and intravenous thrombolysis in atrial fibrillation associated stroke

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ABSTRACT

Background Atrial fibrillation (AF) associated ischemic stroke has worse functional outcomes, less effective recanalization, and increased rates of hemorrhagic complications after intravenous thrombolysis (IVT). Limited data exist about the effect of AF on procedural and clinical outcomes after mechanical thrombectomy (MT).

Objective To determine whether recanalization efficacy, procedural speed, and clinical outcomes differ in AF associated stroke treated with MT.

Methods We performed a retrospective cohort study of the Stroke Thrombectomy and Aneurysm Registry (STAR) from January 2015 to December 2018 and identified 4169 patients who underwent MT for an anterior circulation stroke, 1517 (36.4 %) of whom had comorbid AF. Prospectively defined baseline characteristics, procedural outcomes, and clinical outcomes were reported and compared.

Results AF predicted faster procedural times, fewer passes, and higher rates of first pass success on multivariate analysis ($p < 0.01$). AF had no effect on intracranial hemorrhage (aOR 0.69, 95% CI 0.43 to 1.12) or 90-day functional outcomes (aOR 1.17, 95% CI 0.91 to 1.50) after MT, although patients with AF were less likely to receive IVT (46% vs 54%, $p < 0.0001$).

Conclusions In patients treated with MT, comorbid AF is associated with faster procedural time, fewer passes, and increased rates of first pass success without increased risk of intracranial hemorrhage or worse functional outcomes. These results are in contrast to the increased hemorrhage rates and worse functional outcomes observed in AF associated stroke treated with supportive care and or IVT. These data suggest that MT negates the AF penalty in ischemic stroke.

INTRODUCTION

Atrial fibrillation (AF) remains prevalent, under-treated, and a common cause of acute ischemic stroke (AIS).^{1,2} Large registry studies have demonstrated that comorbid AF is an independent predictor of poor functional outcome and increased

mortality after an ischemic stroke.^{3–6} This is partly explained by covariate older age and medical comorbidities; however, AF associated strokes predicted larger territories of hypoperfusion and larger infarct volumes.^{3,7,8}

The benefit of intravenous thrombolysis (IVT) with alteplase is also modified by comorbid AF. Comorbid AF independently increases the risk of intracranial hemorrhage after IVT, although this may be secondary to the larger infarct burden.^{7,9,10} Consistent with this observation, recanalization rates after IVT have been reported to be lower in AF associated stroke.^{11,12}

Together, these data suggest that the AF associated cardioemboli may have distinct histologic characteristics that underlie these observed clinical differences. The rise of endovascular therapy for AIS has facilitated analysis of acute clots, driving advances in clot science. A number of studies have reported that fibrin-rich thrombi correlate with atheroembolic strokes, whereas erythrocyte-rich thrombi are more often associated with cardioembolic stroke, although this has recently been challenged.^{13–15}

Whether these histologic differences predict responsiveness to mechanical reperfusion remains unclear. A secondary analysis of the MR CLEAN trial reported a non-significant trend towards decreased benefit of mechanical thrombectomy (MT) in patients with AF, while a subsequent meta-analysis demonstrated no interaction between AF and functional outcomes.^{16,17} Similarly, single-center reports have recently reported worse outcomes for AF associated stroke treated with MT for acute large vessel occlusions, secondary to both increased clot size and more resistant clots.¹⁸ Conversely, a national registry study assessing post-thrombectomy outcomes found no difference in either in-hospital or discharge outcomes between patients with or without AF, whereas a separate single-center study suggested higher rates of recanalization with AF associated stroke.^{19,20} Whether AF associated clots are more readily retrievable, or harder to remove, remains unclear.

We therefore aim to assess whether recanalization efficacy, procedural time, and hemorrhagic complications differ in AF associated large vessel occlusions undergoing MT using a large multicenter, international dataset.

METHODS

Study population

Patient data were reviewed from the Stroke Thrombectomy and Aneurysm Registry (STAR), which includes all patients (18 years of age or older) undergoing MT for AIS at 15 comprehensive stroke centers between January 2015 and December 2018. Only patients treated for anterior circulation emergent large vessel occlusions (internal carotid artery, M1, A1 or M2) with modern endovascular devices that were described in the 2015 major thrombectomy trials or after were included. Patients were allocated to the AF group if they had an established diagnosis of AF prior to presentation with AIS, or if AF was diagnosed during the stroke work-up prior to discharge. To guard against confounding comorbid AF and carotid atheroembolism, patients were excluded from analysis if they had both AF and underwent carotid angioplasty or stenting during the thrombectomy. The registry did not assess the completeness of the stroke workup; patients were therefore not excluded due to the presence or absence of any specific diagnostic tests. Additionally, data on antithrombotic use and comorbid heart failure or valvular disease are not currently reported in the registry. This study is covered by approval from institutional review boards at each participating institution, and informed consent was waived given the retrospective design of the study.

Mechanical thrombectomy

Patient selection for MT was based on operator judgment and discussion with patient families. It was not influenced by this study. Participating centers used different selection criteria for patient eligibility. Investigators had no uniform onset-to-groin cut-off point for offering intervention. The frontline thrombectomy approach used was based on operator preference and included aspiration thrombectomy (or a direct aspiration first pass technique), stent retriever, primary combined approach or, in a few cases, intracranial angioplasty and stenting. Success of recanalization was reported using the modified Thrombolysis in Cerebral Infarction (TICI) score obtained by the operator at the end of the procedure.²¹ Postprocedural hemorrhage was assessed using postoperative CT or MRI performed at 24 hours after the procedure.

Data collection

Demographic data, admission deficits, severity scores, onset-to-groin time, and IVT use were reviewed from patient charts. Procedure notes and imaging reports were reviewed for technical variables, reperfusion scores (TICI), and hemorrhage scores. Postprocedural hemorrhage was scored by neuroradiologists based on European Cooperative Acute Stroke Study II (ECASS II) criteria.²² Successful recanalization was defined as a TICI score of 2b or more.

Clinical outcomes

The modified Rankin Scale (mRS) score was the primary outcome measure. mRS scores were obtained during routinely scheduled follow-up visits with stroke neurologists or advanced practice providers at 90-days post-stroke (± 14 days). If patients were discharged to a nursing home or hospice, telephone encounters were used. Telephone encounters with family were

used to confirm mortality of deceased patients. A good outcome was defined as a mRS score 0–2. Postprocedural National Institutes of Health Stroke Scale (NIHSS) scores (within 24 hours), NIHSS at discharge, and/or follow-up were also available for a subset of patients.

Complications

Procedural notes were reviewed for intraoperative complications, including the type of complication and need for intervention. Additionally, postprocedural hemorrhage was evaluated by a neuroradiologist on postoperative CT or MRI imaging (24 hours) based on ECASS II criteria.²² Symptomatic intracranial hemorrhage (sICH) was defined as postprocedural hemorrhage associated with an increase of at least 4 on the NIHSS.

Statistical analysis

Statistical analyses were performed in SPSS v.25 (IBM) and GraphPad Prism 9 (GraphPad, California, USA). Univariate testing was performed using Student's t-test, Mann-Whitney test, or χ^2 test for parametric, non-parametric, and categorical variables, respectively. Multivariate analysis was then performed using independent models for different outcome measures. Variables included in regression included predetermined variables (age, sex, admission NIHSS score, comorbidities) and variables with $p < 0.1$ on univariate testing. To avoid bias in excluding patients with incomplete data, we used multiple imputations to handle missing baseline variables (race, onset-to-groin, sex, and other comorbidities), and Rubin's rule was then used to approximate coefficients. A total of 10 imputations was performed for each model. Logistic regression models were used for categorical variables (eg, good outcome), and linear regression models were used for continuous variables (eg, procedure time). A p value < 0.05 was considered statistically significant.

RESULTS

Demographic data

A total of 5621 patients underwent MT for AIS at 15 stroke centers during the study period, of whom 4169 had an anterior circulation stroke and were included. Among the included subset, 1517 (36.4%) patients had comorbid AF that was diagnosed either before, or at the time of, presentation.

Table 1 reports patient baseline and presentation characteristics. Patients with AF were more likely to be older, female, white, and have vascular risk factors, including hypertension and hyperlipidemia ($p < 0.05$). At presentation, patients with AF had higher NIHSS scores on admission, lower Alberta Stroke Program Early CT Score (ASPECTS), and a lower rate of IVT with tissue plasminogen activator (tPA; $p < 0.05$). There was no difference in onset-to-groin time or pre-stroke mRS scores between the two groups ($p > 0.05$, table 1). The distribution of occluded vessels per group is shown in online supplemental figure 1 and was comparable between the two groups. The majority of patients presented with M1 occlusions (AF vs no AF, 57% vs 56%, $p > 0.05$).

Procedural metrics

Univariate analysis for procedural variables is also shown in table 1, notable for faster procedural time in patients with AF (51 min vs 56 min, $p = 0.002$). Comorbid AF was associated with fewer total number of thrombectomy attempts (mean 2.2 vs 2.4, $p = 0.016$) and a higher rate of first pass success (42% vs 35%, $p = 0.001$). Angiographic outcomes were similar between the two groups, with similar rates of TICI 2b and TICI 3 reperfusion.

Table 1 Patient demographic, admission, technical, radiographic, and clinical outcome variables

Variable	AF		No AF		Test	Standardized mean difference	P value
	N	Mean (SD) Median (IQR) N (%)	N	Mean (SD) Median (IQR) N (%)			
Demographics							
Age	1517	76 (11)	2652	65 (15)	t-test	0.75	0.001
Female	1517	877 (58%)	2651	1299 (49%)	Chi-sq		0.02
White race	1133	754 (67%)	2107	1241 (59%)	Chi-sq		0.001
Comorbidities							
Diabetes	1511	453 (30%)	2650	721 (27%)	Chi-sq		0.06
Hypertension	1517	1252 (83%)	2652	1860 (70%)	Chi-sq		0.001
Hyperlipidemia	1514	668 (44%)	2652	979 (37%)	Chi-sq		0.001
Prior stroke	1070	196 (18%)	1982	287 (14%)	Chi-sq		0.006
Pre-stroke mRS score 0–2	1085	986 (91%)	2022	1871 (93%)	Chi-sq		0.121
Admission variables							
Admission NIHSS score	1502	16 (6)	2630	15 (7)	t-test	0.15	0.001
ASPECTS	1112	8 (2)	1889	9 (3)	MW	0.37	0.015
IV tPA use	1401	651 (46%)	2498	1340 (54%)	Chi-sq		0.001
Onset-to-groin time (hours)	1139	5.9 (7.2)	2147	6.1 (8.4)	t-test	0.02	0.476
Procedural variables							
Procedure time (min)	1331	51 (43)	2382	56 (44)	t-test	0.10	0.002
Total attempts	1368	2.1 (1.6)	2439	2.3 (1.7)	MW	0.12	0.001
First pass success	902	377 (42%)	1574	552 (35%)	Chi-sq		0.001
Final TICl score	1437		2477		Chi-sq		0.301
0–2a		233 (16%)		369 (15%)			
2b–3		1204 (84%)		2108 (85%)			
ICA angioplasty	1437	0 (0.0%)	1481	82 (6%)	Chi-sq		0.001
Complications	909	78 (9%)	1841	157 (9%)	Chi-sq		0.999
Hemorrhage (any type)	1322	300 (23%)	2382	571 (24%)	Chi-sq		0.396
Hemorrhage (PH2/sICH)	1165	89 (8%)	2197	160 (7%)	Chi-sq		0.729
Outcome							
mRS score: discharge	796	4 (3)	1319	3 (3)	MW	0.12	0.001
mRS score: 90 days	1368	4 (2)	2439	3 (3)	MW	0.30	0.001
mRS score 0–2	1368	426 (31%)	2434	1029 (42%)	Chi-sq		0.001
mRS score 3–6	1368	942 (69%)	2434	1405 (58%)	Chi-sq		0.001
Mortality: 90 days	1368	354 (26%)	2434	408 (17%)	Chi-sq		0.001

Statistical tests were done using t-tests, chi squared tests (Chi-sq), or Mann-Whitney (MW) tests. A standardized mean difference >0.10 is considered meaningful.

AF, atrial fibrillation; ASPECTS, Alberta Stroke Program Early CT Score; ICA, internal carotid artery; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH2, parenchymal hematoma type II (ECASS II criteria); sICH, symptomatic intracranial hemorrhage; TICl, thrombolysis in cerebral infarction.

To better determine whether comorbid AF is an independent predictor of faster recanalization and a lower number of attempts, we performed multivariate analyses while controlling for potential confounders (figure 1). Using multivariate linear regression, comorbid AF was an independent predictor of shorter procedure time (adjusted coefficient (−) 5.4, $p < 0.001$) and fewer attempts to achieve recanalization (adjusted coefficient (−) 0.2, $p < 0.001$). On multivariate logistic regression for predictors of first pass success, AF was associated with higher odds of first pass success (adjusted OR=1.29, $p = 0.008$, figure 1). Additional predictors of first pass success and procedure time are reported in figure 1.

Postprocedural hemorrhage

Given the association of AF with sICH after IVT, we also tested whether AF was an independent risk factor for sICH after MT. There was no significant difference in rates of sICH or parenchymatous hematoma type 2 (PH2) between patients with or without

AF with univariate analysis (table 1). On multivariate analysis for predictors of sICH and or PH2 (sICH/PH2), neither IVT nor AF were independent predictors of postprocedural sICH/PH2 in the full cohort or in successfully recanalized patients only (TICl 2b or higher, table 2). Only advanced age and lower ASPECT scores were independently associated with higher rates of sICH/PH2 in the full cohort (table 2).

Functional outcome

On univariate analysis, patients with comorbid AF had worse functional outcomes at discharge along with increased mortality and decreased rates of a good functional outcome at 90 days (table 1). However, patients with AF were significantly older and had worse presenting deficits (table 1). We assessed whether this effect was attributed to confounding variables using multivariate analysis. When controlling for age, admission NIHSS score, and ASPECT scores on admission, AF was not an independent

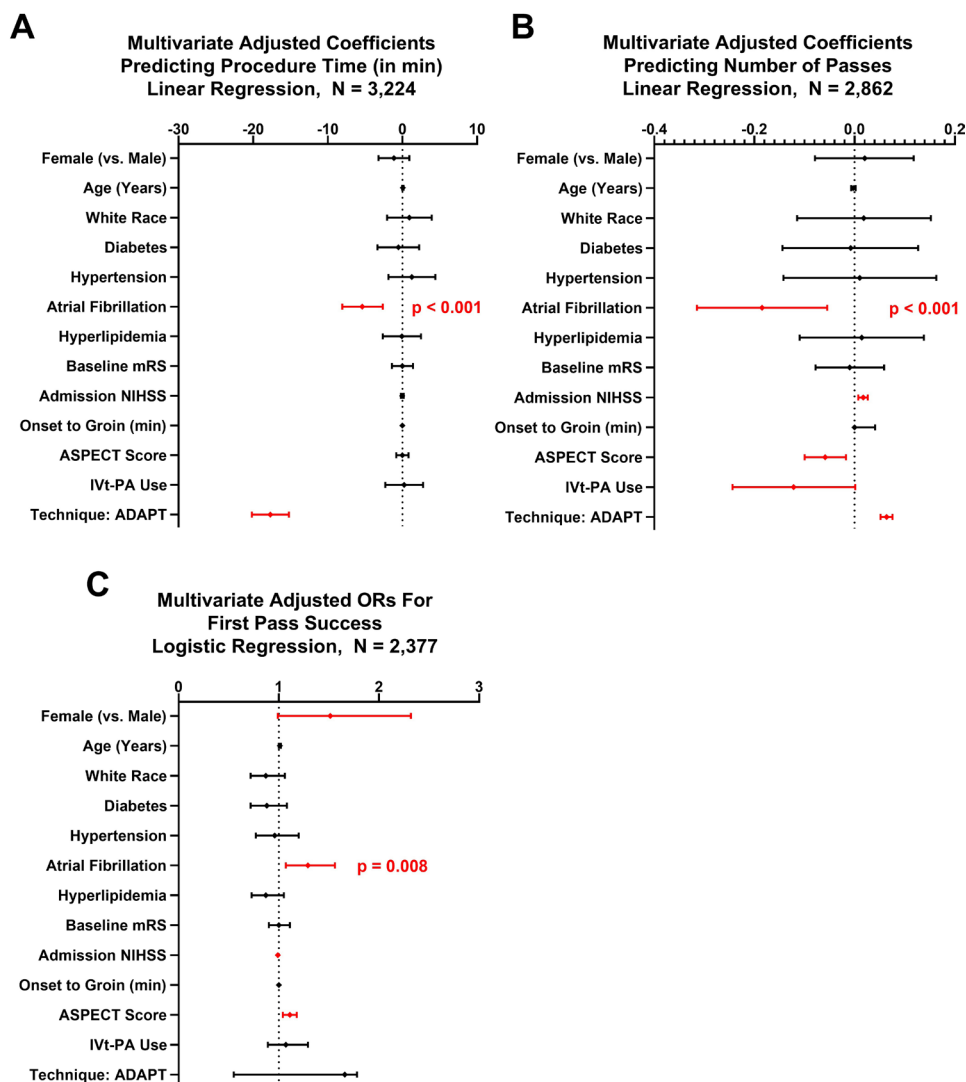


Figure 1 Multivariate regression analyses for predictors of procedure time (A), number of attempts (B), and success of first pass (C). Shown are adjusted ORs or estimates with error bars representing 95% confidence intervals (CIs). Significant estimates ($p < 0.05$) are highlighted in red.

predictor of good outcome at 90 days (aOR 1.17, 0.91–1.50, $p = 0.224$, table 3). This suggests that the worse outcomes observed in AF associated strokes can probably be attributed to poor presenting deficits in addition to advanced age in this group.

DISCUSSION

AF has previously been shown to be associated with worse functional outcomes, larger infarcts, decreased rates of recanalization, and increased rates of hemorrhagic complications after IVT.^{3–6} This has been hypothesized to be due to larger embolized clots, larger territories at risk, and the lack of pre-ischemic conditioning.^{3,7,8,23} Notably, these data come from the IVT era and predate the widespread availability of MT. These associations have not yet been explored in the setting of MT, with or without bridging therapy.

Here, we report for the first time that MT in patients with comorbid AF is associated with faster recanalization time, fewer passes, and higher rates of first pass success. Despite decreased procedural times, patients with AIS with comorbid AF have worse functional outcomes, consistent with observations from the pre-endovascular era.^{3–6} Our data suggest that these worse

outcomes are attributable to increased age, decreased ASPECTS, and more severe deficits at onset, but not AF in adjusted models.

AF has been consistently shown to independently predict intracranial hemorrhage in the pre-endovascular era, with or without IVT.^{3,5,8–10,20} In contrast to these reports, AF is not associated with increased intracranial hemorrhage in patients undergoing MT, either in the full cohort or those who achieved good angiographic reperfusion (table 2). This is even more striking when considering the likely enrichment of anticoagulant use in the AF cohort who underwent MT. In contrast, patients with AF receiving anticoagulants are largely excluded from IVT and are nevertheless more likely to have an intracranial hemorrhage after IVT, further supporting a differential effect of MT and IVT on post-reperfusion hemorrhage rates. Our observations extend the recently reported experiences in randomized controlled trials, demonstrating that AF does not interact with MT outcomes in a large, international registry.

These results also raise a novel question in the ongoing debate about bridging therapy for large vessel occlusions.^{24,25} Given that IVT complications are increased in patients with AF associated stroke, our observation of equivalent clinical and hemorrhagic outcomes with MT raises the question of how AF modifies the

Table 2 Multivariate logistic regression for predictors of postprocedural sICH/PH2 hemorrhage

Variable	Coefficient	95% CI	P value
Full cohort			
Model: logistic regression, n=1823			
Age	1.02	1 to 1.03	0.026
White race	1.06	0.7 to 1.6	0.798
Diabetes mellitus	1.44	0.94 to 2.19	0.090
Hypertension	1.13	0.66 to 1.93	0.655
Hyperlipidemia	1.02	0.68 to 1.54	0.915
Atrial fibrillation	0.76	0.49 to 1.18	0.219
Pre-stroke mRS score 0–2	0.94	0.47 to 1.89	0.867
Admission NIHSS score	1.01	0.98 to 1.04	0.576
IV tPA use	1.32	0.87 to 2	0.189
Onset-to-groin	1.00	0.99 to 1.01	0.290
ASPECTS	0.89	0.79 to 0.99	0.038
Successful recanalization	0.89	0.51 to 1.55	0.674
Attempts	1.02	0.91 to 1.14	0.762
IA tPA	1.28	0.77 to 2.14	0.339
TICI 2b–3 Cohort			
Model: logistic regression, n=1614			
Age	1.02	1.01 to 1.04	0.007
White race	1.03	0.66 to 1.6	0.914
Diabetes mellitus	1.52	0.96 to 2.4	0.071
Hypertension	0.9	0.51 to 1.59	0.724
Hyperlipidemia	1.2	0.77 to 1.86	0.425
Atrial fibrillation	0.69	0.43 to 1.12	0.133
Pre-stroke mRS score 0–2	1	0.47 to 2.16	0.997
Admission NIHSS score	1.01	0.98 to 1.04	0.623
IV tPA use	1.28	0.82 to 2.01	0.283
Onset-to-groin	1	1 to 1	0.385
ASPECTS	0.89	0.78 to 1	0.057
Attempts	0.97	0.85 to 1.1	0.618
IA tPA	1.4	0.81 to 2.4	0.228

ASPECTS, Alberta Stroke Program Early CT Score; IA tPA, intra-arterial tissue plasminogen activator; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH2, parenchymal hematoma type II (ECASS-II criteria); sICH, symptomatic intracranial hemorrhage; TICI, thrombolysis in cerebral infarction.

effect of bridging therapy in these patients.^{7 9 10} The enrichment of IVT complications in patients with AF in the pre-endovascular era suggests that patients with AF may be a particularly high-risk subgroup who may benefit from a direct-to-thrombectomy approach at thrombectomy-capable centers. Further investigation will be needed to assess the efficacy and safety of bridging therapy in these patients.

Strengths of our study include leveraging a large multicenter database with over 5000 thrombectomies, characterizing the real-world experience and outcomes across a spectrum of large academic institutions. Nevertheless, our study has a number of limitations. First, the stroke mechanism in patients without AF was not available for each patient. Instead, we used comorbid AF as a surrogate of the stroke mechanism, probably underestimating the rate of non-cardioembolic stroke in patients with comorbid AF. Estimates vary of the rate of non-cardioembolic strokes that occur in patients with AF, largely due to lacunar or carotid disease.^{26 27} Nevertheless, because we selected for large vessel occlusions, lacunar contributions are unlikely. Additionally, patients with treated carotid disease were excluded

Table 3 Multivariate logistic regression for predictors of good outcome (MRS 0–2) at 90 Days in full cohort

Variable	Coefficient	95% CI	P value
Full cohort controlling for AF			
Model: logistic regression, n=3024			
Age	0.97	0.96 to 0.97	0.001
Diabetes mellitus	0.71	0.55 to 0.91	0.008
Hypertension	0.7	0.53 to 0.91	0.009
Hyperlipidemia	1.3	1.03 to 1.64	0.029
Atrial fibrillation	1.17	0.91 to 1.5	0.224
Pre-stroke mRS score 0–2	7.84	3.96 to 15.52	0.001
Admission NIHSS score	0.9	0.89 to 0.92	0.001
IV tPA use	1.28	1.02 to 1.6	0.034
Onset-to-groin	1	1 to 1	0.734
ASPECTS	1.23	1.14 to 1.32	0.001
Number of attempts	0.79	0.73 to 0.85	0.001
Successful reperfusion (TICI 2b+)	2.51	1.73 to 3.64	0.001

AF, atrial fibrillation; ASPECTS, Alberta Stroke Program Early CT Score; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TICI, thrombolysis in cerebral infarction score.

from the AF cohort. Second, angiographic outcomes (final mTICI), hemorrhagic complications, and functional outcomes were scored locally and not centrally adjudicated. Third, as a retrospective registry, we cannot exclude selection bias, particularly with decisions for continued recanalization attempts to improve the angiographic outcome. Fourth, antithrombotic data are not currently reported in the STAR registry, therefore limiting commentary on the concomitant use of antiplatelets and/or anticoagulants and the risk of hemorrhagic complications. Finally, we did not assess posterior circulation occlusions given the center-to-center variability in inclusion criteria and the paucity of randomized data to guide decision making. Whether these results extend to posterior circulation strokes remains unclear.

CONCLUSIONS

In patients treated with MT, comorbid AF is associated with faster procedural time, fewer passes, and increased rates of first pass success without increased risk of intracranial hemorrhage. These results are in contrast to the increased hemorrhage rates reported in AF associated stroke treated with supportive care and or thrombolysis. Together, these results suggest that AF associated stroke has a differential response to IVT and MT, and that MT negates the AF penalty in ischemic stroke.

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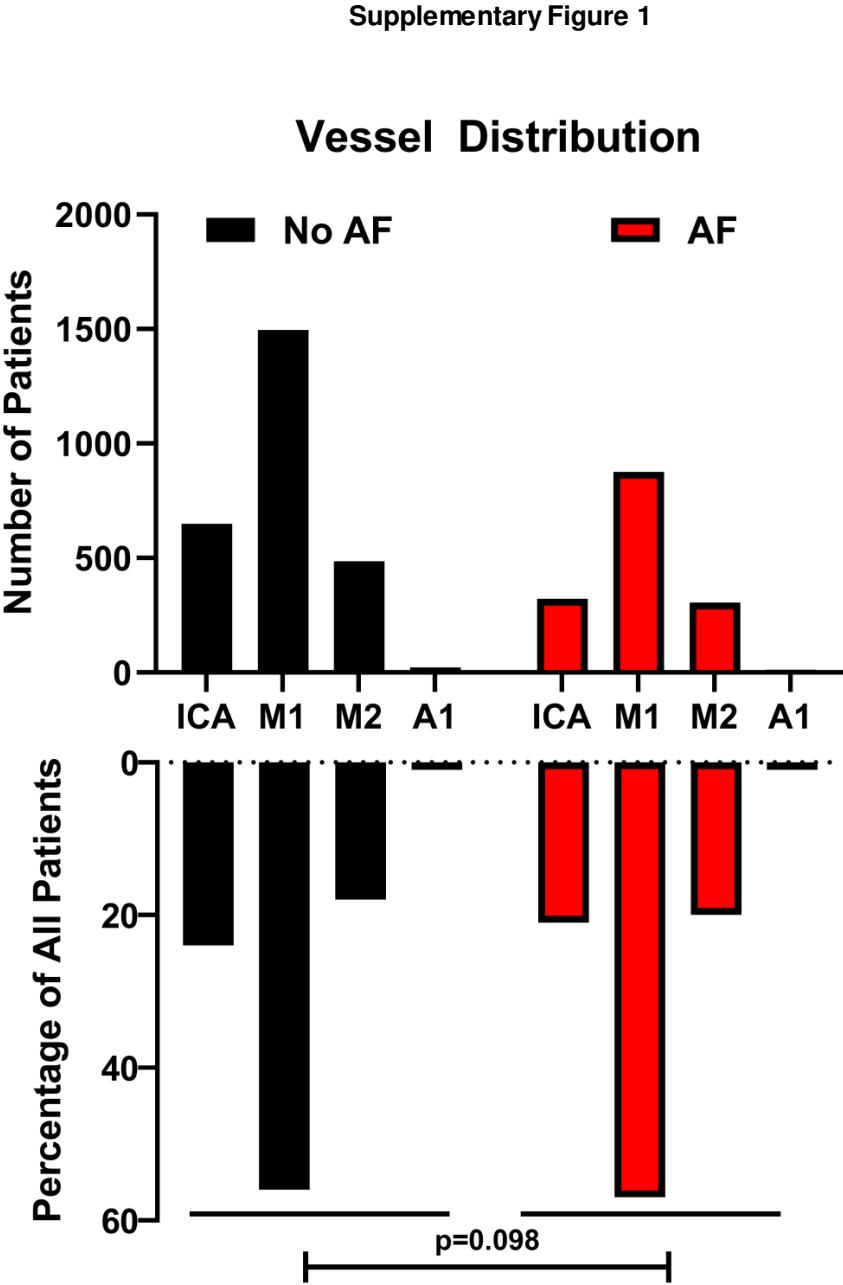
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Supplementary Figure 1. Distribution of thrombectomy patients by vessel and atrial fibrillation status. There was no significant difference in distribution between the groups using a Chi-squared test.