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Effect of atrial fibrillation on endovascular thrombectomy for acute ischemic stroke. A meta-analysis of individual patient data from six randomised trials: Results from the HERMES collaboration

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Abstract

Background: Atrial fibrillation is an important risk factor for ischemic stroke, and is associated with an increased risk of poor outcome after ischemic stroke. Endovascular thrombectomy is safe and effective in acute ischemic stroke patients with large vessel occlusion of the anterior circulation. This meta-analysis aims to investigate whether there is an interaction between atrial fibrillation and treatment effect of endovascular thrombectomy, and secondarily whether atrial fibrillation is associated with worse outcome in patients with ischemic stroke due to large vessel occlusion.

Methods: Individual patient data were from six of the recent randomised clinical trials (MR CLEAN, EXTEND-IA, REVASCAT, SWIFT PRIME, ESCAPE, PISTE) in which endovascular thrombectomy plus standard care was compared to standard care alone. Primary outcome measure was the shift on the modified Rankin scale (mRS) at 90 days. Secondary outcomes were functional independence (mRS 0–2) at 90 days, National Institutes of Health Stroke Scale score at 24 h, symptomatic intracranial hemorrhage and mortality at 90 days. The primary effect parameter was the adjusted common odds ratio, estimated with ordinal logistic regression (shift analysis); treatment effect modification of atrial fibrillation was assessed with a multiplicative interaction term.

Results: Among 1351 patients, 447 patients had atrial fibrillation, 224 of whom were treated with endovascular thrombectomy. We found no interaction of atrial fibrillation with treatment effect of endovascular thrombectomy for

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both primary (*p*-value for interaction: 0.58) and secondary outcomes. Regardless of treatment allocation, we found no difference in primary outcome (mRS at 90 days: aOR 1.11 (95% CI 0.89–1.38) and secondary outcomes between patients with and without atrial fibrillation.

Conclusion: We found no interaction of atrial fibrillation on treatment effect of endovascular thrombectomy, and no difference in outcome between large vessel occlusion stroke patients with and without atrial fibrillation.

Keywords

Ischemic stroke, endovascular thrombectomy, atrial fibrillation, large vessel occlusion

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Introduction

Patients with acute ischemic stroke and atrial fibrillation (AF) present with a higher score on the National Institute of Health Stroke Scale (NIHSS) more frequently have intracranial arterial occlusion(s) and have a worse functional outcome than patients without AF.[1,2] Furthermore, in patients with AF, treatment with intravenous thrombolysis (IVT) is less effective on both recanalisation and clinical outcome.[3,4] Possible explanations are that emboli in AF are larger and show a different pattern of occlusion than emboli due to other causes. Endovascular thrombectomy (EVT) is effective and safe in acute ischemic stroke due to proximal intracranial large vessel occlusion (LVO) of the anterior circulation.[5–7] A post hoc subgroup analysis of the MR CLEAN trial was compatible with decreased treatment effect in patients with AF.[8] However, as only a small number of patients was included in this analysis, the uncertainty of this finding was high. Our aim was to investigate whether AF modifies treatment effect of EVT for acute ischemic stroke due to LVO. Secondarily, we sought to determine whether AF was associated with worse outcome in patients with ischemic stroke due to LVO.

Methods

Data collection

Data are from the "highly effective reperfusion using multiple endovascular devices" (HERMES) collaboration. The HERMES collaboration combined patient level data available from clinical trials that used second-generation mechanical devices (primarily stent retrievers) to test if additional mechanical thrombectomy (intervention group) is better than standard care (control group) in patients with acute ischemic stroke. For this purpose, individual patient data from the MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, PISTE, and THRACE trials were pooled.[5] The HERMES executive committee (comprising representatives of each trial) confirmed that all eligible trials were included and contributed their trial data and the data were collated by an independent biostatistician (SB). All participants or their legal representatives provided informed consent according to each trial protocol and each study was approved by the local ethics board. The meta-analysis was prospectively designed by the HERMES executive committee, but not registered. AF status was known in all of the aforementioned trials but the THRACE trial whose data were therefore excluded.

Outcome measures

The primary outcome was the shift on the modified Rankin Scale (mRS) score at 90 days. The mRS is a score indicating the level of disability ranked between 0–6, with a score of 0–2 associated with functional independence, an increased level of disability with a score of 3–5, and a score of 6 indicating death. Secondary outcome measures were functional independence, defined as mRS 0–2 at 90 days, and stroke severity, measured with the NIHSS score, at 24 h after stroke onset. Safety outcomes were symptomatic intracranial hemorrhage (sICH) and mortality at 90 days. The endpoints in the individual studies were measured in person or by (telephone) interview; raters were blinded to the study arm.

Clinical definitions

The diagnosis of AF was made when patient history was positive for AF, or when AF was diagnosed during hospital stay.

Statistical analysis

We performed an individual patient-level meta-analysis based on the intention-to-treat principle. The primary

effect parameter was the adjusted common odds ratio (acOR), estimated with ordinal logistic regression (shift analysis). We assessed treatment effect modification by AF with a multiplicative interaction variable on both the primary and secondary outcomes. We adjusted the primary and secondary effect parameters for potential imbalances in major pre-specified confounding variables (age, stroke severity (NIHSS) at baseline, treatment with IVT, localisation of occlusion and time from onset to randomisation). We reported adjusted and unadjusted common odds ratios with 95% confidence interval (CI). We analysed binary outcomes with logistic and linear regression respectively, and reported as adjusted and unadjusted odds ratios or betas with 95% CIs, where applicable. All reported *p*-values are two-sided. We performed all statistical analyses SAS software, version 9.3, and R, version 3.2.

Results

In the six trials (MR CLEAN, EXTEND-IA, REVASCAT, SWIFT PRIME, ESCAPE, PISTE), 1351 patients were included. Data on 90-day follow-up were missing in 10 patients (Figure S1). AF was present in 447 patients (33.1%) of whom 224 (50%) were treated with EVT. At baseline, patients with AF were older, less often treated with IVT, had a higher ASPECTS score and more frequently suffered from hypertension (Table 1, Table S1).

There was no significant difference in the treatment effect size of EVT (acOR 2.39 (95% CI 1.47, 3.88) in AF patients, acOR 2.34 (95% CI 1.66, 3.31) in patients without AF) and no interaction of AF with treatment effect of EVT (*p*-value for interaction 0.58) (Table 2, Table S2). We also found no difference in functional outcome between patients with and without AF (aOR 1.11 (95% CI 0.89, 1.38) (Table 3). For the secondary outcomes, there was a trend towards a lower rate of symptomatic intracranial hemorrhage in patients with AF (aOR 0.57 (95% CI 0.3, 1.07)) (Table 3).

Discussion

In this individual patient data meta-analysis, we found no significant modification of the effect of EVT by AF on functional outcome, and secondary outcomes (functional independence at 90 days, NIHSS score at 24 h, symptomatic intracranial hemorrhage and mortality at 90 days). Additionally, in these patients with LVO, the risk of poor outcome was not increased in patients with AF.

A subgroup analysis of the MR CLEAN trial showed a trend towards a lower treatment effect of EVT in patients with AF.[8] However, the number of patients with AF in this study was rather low, therefore no definite conclusion could be drawn. A meta-analysis of 11 randomised controlled trials (RCT) comparing EVT versus standard care found that good functional outcome (mRS 0–2 at 90 days) after EVT occurred more often in patients with AF.[9] These meta-analyses, however, also included several older, neutral trials and did not adjust for treatment with IVT and other potential confounders.

Our finding that in stroke patients with LVO of the anterior circulation there is no difference in functional outcome between patients with and without AF, is in contrast with results of earlier studies in patients with ischemic stroke in general, which found that patients with AF had a worse clinical outcome, even after IVT.[3,4] However, in these studies populations with other stroke types such as atherothrombotic or lacunar strokes were included. Patients with AF more frequently suffer from proximal arterial occlusions, which overall leads to a poorer outcome than other types of ischemic stroke. A likely explanation for our finding is that we only looked at the subset of patients with LVO, and that the underlying mechanism has less influence on stroke severity and outcome than the LVO itself. The finding that baseline NIHSS does not significantly differ between patients with AF and those without supports this notion.

We found a trend towards a lower rate of intracranial hemorrhage in patients with AF (4.5% in patients without AF vs 3.4% in patients with AF). However, this difference did not reach significance (aOR 0.57; 95% CI 0.3–1.07). A significantly lower percentage of AF subjects received IVT compared to patients without AF (76.3% vs 90.6%). At baseline, patients with AF were treated with tPA significantly less frequent than patients without AF. This is likely due to the fact that patients with AF are more likely to use oral anticoagulation, which is a contra-indication for the administration of tPA.

Our results could imply that the lower percentage of sICH in the AF group might be related to the lower percentage of pre-treatment with IVT. The percentage of sICH after treatment with IVT is around 5%.[10] Considering this finding, the question arises whether in patients with a proximal arterial occlusion treatment with IVT prior to EVT is beneficial. Recent observational studies report conflicting results, some reporting that pre-treatment with IVT before EVT is beneficial for outcome,[7,11,12] while others note there is no clear benefit of pre-treatment while the risk of intracranial hemorrhage is higher.[13,14] Another issue is the delay pre-treatment with IVT causes in patients also treated with EVT. The main limitation of these studies is the observational and retrospective design. Therefore, more research into the benefit of IVT in patients with proven LVO eligible for EVT is needed. Currently,

Table 1. Baseline characteristics by AF status and treatment allocation.

	AF		No AF	
Characteristic	Control Mean ± SD (N) [Median] (IQR) OR % (n/N)	EVT Mean ± SD (N) [Median] (IQR) OR % (n/N)	Control Mean ± SD (N) [Median] (IQR) OR % (n/N)	EVT Mean ± SD (N) [Median] (IQR) OR % (n/N)
Age (years)	72.8 ± 9.4 (223) [74.0] (67.0, 79.0)	72.8 ± 10.1 (224) [73.0] (67.0, 80.1)	63.6 ± 13.6 (459) [64.7] (55.0, 74.0)	63.1 ± 13.7 (443) [63.0] (54.0, 74.0)
Female gender	49.8% (111/223)	47.8% (107/224)	44.8% (206/460)	49.0% (217/443)
NIHSS at baseline	16.8 ± 5.4 (223) [17.0] (14.0, 20.5)	17.5 ± 4.8 (223) [18.0] (14.5, 21.0)	16.9 ± 5.7 (457) [17.0] (13.0, 21.0)	16.5 ± 5.2 (440) [17.0] (13.0, 20.0)
tPA delivered	79.4% (177/223)	73.2% (164/224)	92.0% (424/461)	89.2% (395/443)
Diabetes mellitus	17.9% (40/223)	21.0% (47/224)	17.6% (81/461)	15.1% (67/443)
Hypertension	74.9% (167/223)	68.8% (154/224)	51.6% (238/461)	48.5% (215/443)
ASPECTS at baseline	8.1 ± 1.7 (219) [8.0] (7.0, 9.0)	8.0 ± 1.7 (222) [8.0] (7.0, 9.0)	7.6 ± 1.9 (452) [8.0] (7.0, 9.0)	7.7 ± 1.7 (439) [8.0] (7.0, 9.0)
Occlusion location				
Not available	7.2% (16/223)	6.3% (14/224)	5.6% (26/461)	4.7% (21/443)
ICA	24.2% (54/223)	27.2% (61/224)	29.3% (135/461)	27.8% (123/443)
M1	61.0% (136/223)	55.8% (125/224)	55.7% (257/461)	58.5% (259/443)
M2	7.6% (17/223)	10.7% (24/224)	9.3% (43/461)	8.8% (39/443)
Other	0.0% (0/223)	0.0% (0/224)	0.0% (0/461)	0.2% (1/443)
Onset of tPA	125.0 ± 66.4 (178) [110.0] (80.0, 147.8)	115.7 ± 50.8 (162) [105.0] (75.3, 139.3)	116.1 ± 60.9 (424) [100.0] (75.0, 145.0)	111.5 ± 47.3 (395) [102.0] (75.0, 135.0)
Onset of randomisation	213.4 ± 96.1 (223) [196.0] (139.0, 277.0)	212.7 ± 104.9 (224) [191.0] (137.8, 257.5)	208.4 ± 88.7 (458) [191.5] (141.3, 264.0)	210.4 ± 99.3 (441) [193.0] (142.0, 253.0)

AF: atrial fibrillation; NIHSS: National Institutes of Health Stroke Scale; tPA: tissue plasminogen activator; ASPECTS: Alberta Stroke Program Early CT Score; ICA: internal carotid artery; SD: standard deviation; AF: atrial fibrillation; EVT: endovascular thrombectomy.

Table 2. Primary outcome, secondary outcomes, and *p*-value for interaction by AF status and treatment allocation.

		Unadjusted value (95% CI)			Adjusted value (95% CI)		
	Effect	AF	No AF	P inter-action	AF	No AF	P inter-action
mRS score at 90 days	cOR	2.10 (1.33, 3.30)	2.21 (1.66, 2.94)	0.848	2.39 (1.47, 3.88)	2.34 (1.66, 3.31)	0.581
mRS score of 0–2 at 90 days	OR	1.99 (1.32, 2.99)	2.50 (1.88, 3.31)	0.350	2.41 (1.50, 3.85)	2.64 (1.96, 3.56)	0.544
NIHSS at 24 h	Beta	−2.96 (−5.12, −0.80)	−3.50 (−4.58, −2.41)	0.729	−3.50 (−5.74, −1.26)	−3.68 (−5.82, −1.54)	0.686
sICH	OR	1.15 (0.40, 3.35)	1.01 (0.54, 1.90)	0.848	1.09 (0.36, 3.30)	1.04 (0.55, 1.96)	0.900
Mortality at 90 days	OR	0.76 (0.47, 1.23)	0.86 (0.53, 1.40)	0.812	0.69 (0.41, 1.17)	0.89 (0.55, 1.45)	0.536

Results are unadjusted and adjusted for age, NIHSS at baseline, IVT, localisation of occlusion and time from onset to randomisation.
mRS; modified Rankin scale; AF: atrial fibrillation; NIHSS: National Institutes of Health Stroke Scale; sICH: symptomatic intracranial hemorrhage.

there are several ongoing trials investigating this issue (MR CLEAN NO-IV, DIRECT-MT, SWIFT DIRECT, and DIRECT SAFE).

Strengths of this meta-analysis are the large number of included of patients and the high prevalence of AF (1351, 33% AF), leading to more reliable estimations. Also, the uniform documentation of baseline characteristics and outcome measures is a strength.

A limitation of this meta-analysis is that the presence of AF was documented in a binary way, meaning it is not certain whether the patients were known with AF before EVT, and whether it was paroxysmal or chronic. Also, the duration of cardiac monitoring was not recorded; therefore it cannot be excluded that the monitoring varied between studies and individual patients resulting in a diagnosis bias. Another limitation is that data on anticoagulation status were not available for all subjects, as there was no standardised collection of such data across the studies that were included in this meta-analysis. However, the fact that fewer patients with AF were concurrently treated with intravenous thrombolysis may suggest that many AF patients were anticoagulated and therefore ineligible for intravenous thrombolysis treatment. Furthermore, no information on recurrent strokes following the initial event was recorded. This would have been interesting data, considering the fact that in the initial period following an ischemic stroke patients might temporarily not be treated with anticoagulation, possibly leading to a higher recurrence of ischemic stroke in this patient group. However, as we found no difference in outcome between patients with and without AF in this study, we can deduce that a possibly higher rate of recurrence in AF patients did not lead to an overall worse functioning at three months, when compared to patients without AF. Lastly, the included data were derived from randomised controlled trials randomising for EVT plus standard treatment or standard treatment alone; there was no stratification by AF status and therefore, unmeasured confounders cannot be ruled out.

Conclusion

We found no interaction of AF with effect of EVT in patients with AIS due to LVO. Furthermore, we found no difference in the functional outcome between patients with and without AF regardless of treatment, suggesting that the cause of proximal arterial occlusion does not influence outcome in AIS due to LVO. Altogether, our data implies AF status should not influence the decision to proceed to EVT.

Table 3. Primary outcome, secondary outcomes, and *p*-value for interaction by AF status, independent of treatment allocation.

	Effect	*N*	Unadjusted value (95% CI) AF vs no AF	Adjusted value (95% CI) AF vs no AF	*p*-Value (main effect of AF)
Modified Rankin score (mRS) at 90 days	cOR	1341	0.73 (0.59, 0.89)	1.11 (0.89, 1.38)	0.372
Functional independence (mRS 0–2) at 90 days	OR	1341	0.82 (0.64, 1.05)	1.14 (0.87, 1.51)	0.337
NIHSS score at 24 h	Beta	1309	0.46 (–0.47, 1.39)	–0.36 (–1.23, 0.52)	0.423
Symptomatic ICH	OR	1351	0.80 (0.44, 1.47)	0.57 (0.3, 1.07)	0.082
Mortality at 90 days	OR	1341	1.86 (1.39, 2.49)	1.14 (0.83, 1.57)	0.410

Results are unadjusted, and adjusted for age, baseline NIHSS, treatment with IVT, treatment with EVT, localisation of occlusion and time from onset to randomisation. Results include a random effect to capture between-study variance. Odds ratios show results for AF versus non-AF, meaning that an odds ratio > 1 indicates greater probability of the outcome in AF subjects.
AF: atrial fibrillation; NIHSS: National Institutes of Health Stroke Scale; OR: odds ratio; cOR: common odds ratio.

Contributorship

AS, IR, RvO authored the article. Primary statistical analysis was done by SB. All authors reviewed and edited the article and approved the final version of the article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Each trial used in this meta-analysis was approved by the local medical ethical committee.

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Guarantor

RvO.

Informed consent

All participants provided informed consent according to each trial protocol.

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Supplemental Material

Supplemental material for this article is available online.

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