Safety and efficacy of periprocedural antithrombotics in patients with successful reperfusion after endovascular stroke treatment

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Safety and efficacy of periprocedural antithrombotics in patients with successful reperfusion after endovascular stroke treatment

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Objectives: We aimed to evaluate whether the overall harmful effect of periprocedural treatment with aspirin or heparin during endovascular stroke treatment is different in patients with a successful reperfusion after the procedure. *Materials and methods:* We performed a post-hoc analysis of the MR CLEAN-MED trial, including adult patients with a large vessel occlusion in the anterior circulation eligible for endovascular treatment (EVT). In this trial, patients were randomized for periprocedural intravenous treatment with aspirin or no aspirin (1:1 ratio), and for moderate-dose unfractionated heparin, low-dose unfractionated heparin or no unfractionated heparin (1:1:1 ratio). We tested for interaction between the post-EVT extended thrombolysis in cerebral infarction (eTICI) score and treatment with periprocedural medication with multivariable regression analyses. The primary outcome was the modified Rankin Scale score at 90 days. Secondary outcomes were final infarct volume, intracranial hemorrhage, and symptomatic intracranial hemorrhage. *Results:* Of 534 included patients, 93 (17%) had a post-EVT eTICI score of 0-2a, 115 (22%) a score of 2b, 73 (14%) a score of 2c, and 253 (47%) a score of 3. For both aspirin and heparin, we found no interaction between post-EVT eTICI score and treatment on the modified Rankin Scale score (p=0.76 and p=0.47, respectively). We found an interaction between post-EVT eTICI score and treatment with heparin on the final infarct volume (p=0.01). Of note, this interaction showed a biologically implausible distribution over the subgroups. *Conclusions:* The overall harmful effect of periprocedural aspirin and unfractionated heparin is not different in patients with a successful reperfusion after EVT.

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Introduction

With the introduction of endovascular treatment (EVT), the outcome of ischemic stroke patients with an intracranial large vessel occlusion has improved. However, a considerable proportion of patients still has poor functional outcome.[1] Amongst other factors, incomplete microvascular reperfusion and thrombotic complications of endovascular procedure are considered to be hampering clinical recovery.[2,3]It is hypothesized that periprocedural antithrombotic treatment could improve microvascular reperfusion and reduce thrombotic complications.[4,5] However, the recent MR CLEAN-MED trial showed that routine use of periprocedural aspirin or unfractionated heparin during endovascular stroke treatment is associated with an increased risk of symptomatic intracranial hemorrhage (ICH), without a benefit on functional outcome.[6] These results do not correspond to earlier observational studies suggesting a beneficial effect, despite a slightly increased risk of symptomatic ICH.[4] A post-hoc analysis of the MR CLEAN trial showed that a favorable effect of successful angiographic reperfusion on functional outcome was especially observed in patients on prior antiplatelet use.[7] In addition, the CHOICE trial found that the use of adjunct intra-arterial alteplase resulted in a greater likelihood of excellent neurological outcome in patients with successful reperfusion following EVT.[8] This may indicate that the treatment effect of periprocedural use of antithrombotics is influenced by post-EVT reperfusion status, and that it may be safe and effective to start periprocedural aspirin or unfractionated heparin in the subgroup of patients with a successful reperfusion.

We aimed to evaluate whether the overall harmful effect of periprocedural treatment with aspirin or unfractionated heparin during endovascular stroke treatment is different in patients with a successful reperfusion after the procedure.

Patients & methods

Study design and patients

We performed a post-hoc analysis of data from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN)-MED.[6] This was a phase III multicenter clinical trial with randomized group assignment, open-label treatment, and blinded outcome evaluation. Patients were included from January 2018 until January 2021 in 15 centers in the Netherlands. The trial included adult patients (i.e. ≥18 years) with ischemic stroke due to a large vessel occlusion in the anterior circulation (i.e. the intracranial part of the internal carotid artery [ICA], or the middle cerebral artery segment M1 or proximal M2) eligible for EVT within 6 hours of stroke onset. Patients were randomized for periprocedural intravenous treatment with aspirin (300 mg bolus) or no aspirin (1:1 ratio), and for moderate-dose unfractionated heparin (5000 IU bolus followed by 1250 IU/hour for 6 h), low-dose unfractionated heparin (5000 IU bolus followed by 500 IU/hour for 6 hours) or no unfractionated heparin (1:1:1 ratio). All study treatments were started directly after groin puncture or – if continuous infusion of intravenous thrombolytics was still ongoing during groin puncture – after the infusion of intravenous thrombolytics was completed. Both treatments had to be started before the endovascular procedure was terminated (i.e., before closure of the groin puncture site). In case an untoward event occurred (e.g., perforation or hemorrhage), the decision to stop the study medication was left to the discretion of the treating physician. The trial used a deferred consent procedure in accordance with national legislation.[9] For the current analysis, we selected patients with deferred consent for 3-month clinical follow-up and available post-EVT extended treatment in cerebral infarction (eTICI) score.

The protocol of the MR CLEAN-MED trial was published previously.[10] The study protocol was approved by a central medical ethics committee at Erasmus MC University Medical Center. The trial was stopped early for safety concerns with the study treatments. De-identified data collected for the study will be made available to others upon reasonable request. Data can be requested with a proposal at the website of the CONTRAST consortium (www.contrast-consortium.nl), or by sending an e-mail to the corresponding author.

Outcomes

In the MR CLEAN-MED trial, clinical outcomes, including modified Ranking Scale (mRS) score at 90 days, were collected centrally by trained research nurses through standardized telephone interviews. Independent committees, masked to treatment allocation, adjudicated serious adverse event reports and primary outcome data based on the interview reports. Imaging outcomes were assessed with standardized case report forms by an imaging committee masked to all clinical data except to the side of stroke. The eTICI score was used to rate the post-EVT reperfusion status. The eTICI score ranges from grade 0 to grade 3, with grade 0 indicating 0% reperfusion of macrovascular vessels on digital subtraction angiography

(DSA), and grade 3 indicating 100% reperfusion. To determine the post-EVT eTICI score, a complete anterior-posterior and lateral angiogram (of the whole head and including the venous phase) at the end of the endovascular procedure had to be available. Final infarct volume was determined using automated validated software (Nicolab, Amsterdam, Netherlands).[11] In order of availability, it was assessed with MRI at 5-7 days, non-contrast CT at 5−7 days, MRI at 24 h or non-contrast CT at 24 h. ICH occurrence was assessed on standard follow-up imaging (CT or MRI) at 24 hours or 5-7 days after EVT, or on additional imaging performed by the treating physician (e.g., after neurological deterioration). ICH was classified as symptomatic based on the Heidelberg Bleeding Criteria (neurological deterioration related to ICH with an increase of ≥ 4 points on the National Institutes of Health Stroke Scale [NIHSS], or ≥ 2 points on 1 NIHSS item).

Statistical analysis

Descriptive characteristics were presented stratified for post-EVT eTICI scores. The effect of aspirin and unfractionated heparin (low dose or moderate dose) on the modified Rankin Scale (mRS) score at 90 days was estimated with multivariable ordinal logistic regression based on intention to treat, in the overall population included in the current study and stratified for post-EVT eTICI scores. To test for interaction, we added an interaction term between periprocedural treatment with aspirin or unfractionated heparin and post-EVT eTICI score. As secondary analyses, we also evaluated the effect on final infarct volume (linear regression), ICH (binary logistic regression), and symptomatic ICH (binary logistic regression). The effects were presented as unadjusted and adjusted common odds ratios, odds ratios, or betas. The presented betas reflect the effect of treatment on final infarct volume in milliliters. Analyses were adjusted for age, pre-stroke mRS, baseline NIHSS, baseline Alberta Stroke Programme Early CT Score (ASPECTS), baseline collateral score, time from onset to groin puncture, and most proximal occlusion location on first DSA. Post-EVT eTICI scores of 0-2a were merged into one subgroup, due to the low proportion of patients in these individual categories. The interaction terms and effects stratified for post-EVT eTICI score are of main interest for the current research question. Effects in the overall population on which the interaction terms were based, were additionally estimated and presented for correct interpretation of these results.

All statistical analyses were performed using R version 4.0.5. (www.cran.r-project.org) with the packages: *Hmisc, rms, tableone*. For multivariable regression analyses, we replaced missing independent variables with multiple imputation using the aregImpute function. We generated 5 multiple imputation sets, in which we used 3 knots for continuous variables. In the model we included outcome variables without missing data (i.e., mRS at 90 days, and symptomatic ICH).

Results

Patients

Six hundred sixty-three patients were randomized in the MR CLEAN-MED trial, of whom 628 patients gave deferred consent for primary outcome assessment (Fig. 1). Of these 628 patients, we excluded 94 who had no

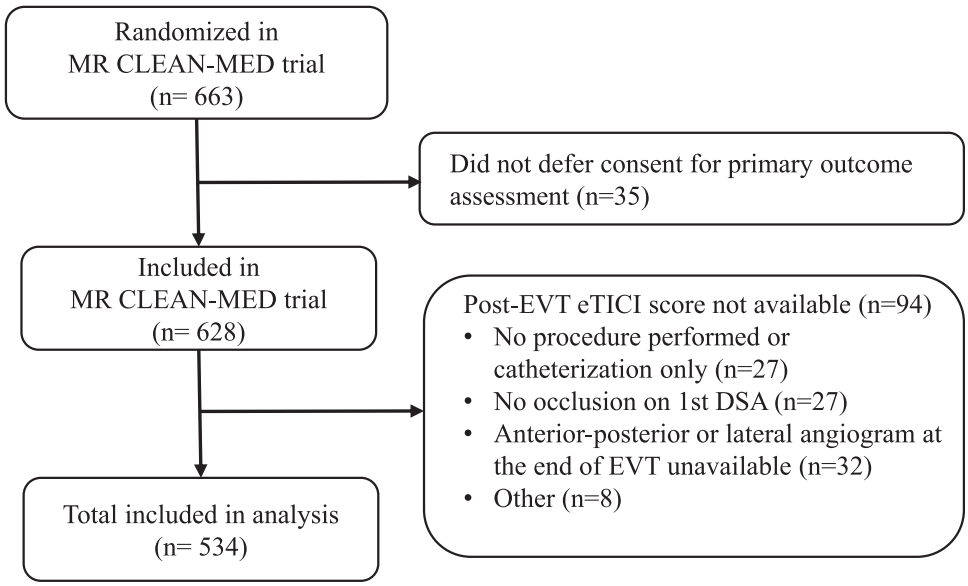

Fig. 1. *Flowchart of patients included for the analysis.*
EVT indicates endovascular treatment; eTICI score indicates extended thrombolysis in cerebral infarction score; DSA indicates digital subtraction angiography

available post-EVT eTICI score. In total, 534 patients were available for the analysis.

Patient characteristics

Median age was 73 (interquartile range [IQR] 64-81) years, 285 (53%) patients were men, median baseline NIHSS score was 15 (IQR 9-19), median baseline ASPECTS was 9 (IQR 8-10), and 390 (73%) patients were treated with intravenous thrombolytics (Table 1). On the first DSA of endovascular procedure, most patients had an M1 (49%) occlusion, followed by an M2 (28%), ICA (18%) or other (5%) occlusion. Median onset to groin puncture time was 175 (IQR 145−225) minutes, and median duration of procedure was 48 (IQR 30-70) minutes. Of 529 patients with complete data on periprocedural aspirin treatment, 235 (44%) were treated with periprocedural aspirin, and of 532 patients with complete data on unfractionated heparin treatment, 266 (50%) were treated with periprocedural unfractionated heparin. Of the 534 included patients, 93 (17%) had a post-EVT eTICI score of 0-2a, 115 (22%) a score of 2b, 73 (14%) a score of 2c, and 253 (47%) a score of 3. In total, 52/8010 (0.6%)

Table 1. *Baseline characteristics of the study population, stratified by post-EVT eTICI score.*

	Post-EVT eTICI 0-2a (*n* = 93)	Post-EVT eTICI 2b (*n* = 115)	Post-EVT eTICI 2c (*n* = 73)	Post-EVT eTICI 3 (*n* = 253)	Missings
Age, years; median [IQR]	74 [64−82]	75 [64−81]	72 [66−80]	72 [64−81]	0
Men, n (%)	48 (52)	60 (52)	40 (55)	137 (54)	0
Transferred from primary hospital, n (%)	76 (82)	89 (77)	54 (74)	204 (81)	0
NIHSS score; median [IQR]	12 [8-18]	17 [9-20]	16 [11-19]	15 [9-19]	20
Medical history, n (%)					
Atrial fibrillation	21 (23)	21 (18)	21 (29)	69 (27)	0
Hypertension	39 (42)	53 (46)	33 (45)	113 (45)	0
Ischemic stroke	20 (22)	17 (15)	12 (16)	49 (19)	1
Prior antithrombotic drug use, n (%)					
Antiplatelets	35 (38)	40 (35)	26 (36)	61 (24)	0
Direct oral anticoagulant	11 (12)	7 (6.1)	7 (9.6)	28 (11)	0
Coumarine	6 (6.5)	11 (9.6)	11 (15)	29 (12)	0
Heparin	1 (1.1)	0 (0.0)	0 (0.0)	4 (1.6)	0
Pre-stroke mRS score, n (%)					2
0	59 (64)	80 (70)	53 (73)	171 (68)	
1	16 (17)	21 (18)	12 (16)	42 (17)	
2	12 (13)	11 (9.6)	4 (5.5)	22 (8.7)	
≥3	5 (5.4)	3 (2.6)	4 (5.5)	17 (6.7)	
Intravenous alteplase treatment, n (%)	69 (74)	80 (70)	49 (67)	192 (76)	0
ASPECTS on NCCT; median [IQR]	9 [8−10]	9 [7-10]	9 [8−10]	9 [8−10]	3
Right hemisphere occlusion, n (%)	49 (53)	46 (40)	37 (51)	132 (52)	0
Proximal occlusion on CTA, n (%)					2
ICA	10 (11)	3 (2.6)	9 (13)	23 (9.1)	
ICA-T	10 (11)	22 (19)	13 (18)	49 (19)	
M1-segment	45 (48)	61 (53)	39 (54)	129 (51)	
M2-segment	28 (30)	29 (25)	11 (15)	51 (20)	
Proximal occlusion on first DSA, n (%)					4
ICA	12 (13)	16 (14)	18 (25)	50 (20)	
M1-segment	28 (30)	54 (47)	41 (57)	137 (54)	
M2-segment	38 (41)	35 (31)	13 (18)	62 (25)	
Other (M3/M4/anterior)	14 (15)	9 (7.9)	0 (0.0)	3 (1.2)	
Occlusion of ipsilateral carotid artery, n (%)	13 (15)	14 (12)	15 (21)	39 (16)	7
Good collateral score (>50%), n (%)	34 (37)	42 (37)	25 (34)	96 (38)	3
Time from onset to groin puncture, minutes; median [IQR]	181 [158-247]	185 [153-248]	168 [137-195]	167 [140-218]	13
Periprocedural aspirin given, n (%)	36 (39)	55 (49)	28 (38)	116 (46)	5
Periprocedural unfractionated heparin given, n (%)	48 (52)	59 (51)	35 (48)	124 (49)	2

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as frequencies (n) and percentages (%). EVT indicates endovascular treatment; eTICI, extended thrombolysis in cerebral infarction; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; ASPECTS, Alberta Stroke Program Early CT Score; NCCT, non-contrast CT; CTA, CT-angiography; ICA (-T), internal carotid artery (terminus);M (segment), middle cerebral artery;

Table 2. *Primary and secondary outcomes of the study population, stratified by post-EVT eTICI score.*

	Post-EVT eTICI 0-2a (*n* = 93)	Post-EVT eTICI 2b (*n* = 115)	Post-EVT eTICI 2c (*n* = 73)	Post-EVT eTICI 3 (*n* = 253)	Missings
Modified Rankin Scale Score at 90 days; median [IQR]	3 [2−6]	2 [1−5]	2 [1-4]	2 [1−5]	0
Final infarct volume on NCCT or MRI, mL; median [IQR]	42 [6.6−119]	37 [8.2−88]	21 [5.3−44]	19 [3.2−80]	94
Intracranial hemorrhage, *n* (%)	37 (46)	61 (57)	25 (39)	104 (46)	56
Symptomatic intracranial hemorrhage, *n* (%)	7 (7.5)	12 (10)	8 (11)	28 (11)	0

Continuous variables are presented as median and interquartile range (IQR). Categorical variables are presented as frequencies (n) and percentages (%). EVT indicates endovascular treatment; eTICI, extended thrombolysis in cerebral infarction; NCCT, non-contrast CT; MRI, magnetic resonance imaging

data points of independent variables included in the regression analyses were missing and imputed.

Outcomes

Median mRS score at 90 days was 2 (IQR 1-5), and median final infarct volume was 24 (IQR 5-81) ml (Table 2). Of 478 patients with available follow-up imaging, 227 (48%) patients had an ICH, and of 534 included patients, 55 (10%) had a symptomatic ICH. Patients with worse post-EVT eTICI scores had higher final infarct volumes. In 56 (10%) patients ICH occurrence could not be assessed as no follow-up imaging was performed, and in 94 (18%) patients final infarct volume could not be assessed as no follow-up imaging with good enough quality to assess infarct volume was performed.

Interactions

Results of univariable analyses (Supplementary Figs. 1 and 2) were comparable to the results of multivariable analyses (Figs. 2 and 3). There was no overall effect of aspirin (adjusted common odds ratio [acOR] 0.94; 95% CI 0.69-1.28) or unfractionated heparin (acOR 0.87; 95% CI 0.64-1.19) on the mRS score at 90 days. For aspirin, there was an overall significant increase in ICH (acOR 1.52; 95% CI 1.04-2.22), and symptomatic ICH (acOR 2.24; 95% CI 1.22-4.10). For unfractionated heparin, there was an overall significant increase in symptomatic ICH (acOR 2.12; 95% CI 1.15-3.88). There was no indication of treatment effect heterogeneity across eTICI scores. For both aspirin and unfractionated heparin, we found no interaction between post-EVT eTICI score and the treatment effect on mRS (p = .76, and p = .47, respectively), ICH (p = .69, and *p* = .12), and symptomatic ICH (p = .28, and p = .57). For unfractionated heparin, we found an interaction between post-EVT eTICI score and treatment on the final infarct volume (p = .010). The point estimate of the treatment effect of unfractionated heparin on final infarct volume was beneficial in patients with a post-EVT eTICI score 2b and harmful in patients with a post-EVT eTICI score 0-2a, 2c, or 3.

Discussion

In this post-hoc analysis of the MR CLEAN-MED trial, we found no convincing evidence that the reperfusion status after endovascular stroke treatment influences the efficacy and safety of periprocedural treatment with intravenous aspirin or unfractionated heparin.

Periprocedural antithrombotics are often used in endovascular procedures for a variety of indications.[12−14] This treatment strategy has been adopted by many interventionists in the endovascular treatment of acute ischemic stroke.[4,15] However, the safety and efficacy of periprocedural antithrombotic agents for this indication has long remained unknown. This was until the MR CLEAN-MED trial − the first randomized controlled trial investigating the safety and efficacy of periprocedural antithrombotic agents during endovascular stroke treatment − found an increased risk of symptomatic ICH, without a beneficial effect on functional outcome.[16] Earlier observational studies had indicated a potential interaction with post-EVT reperfusion status.[7] This led to the hypothesis that the safety and efficacy of periprocedural antithrombotic agents could be influenced by the post-EVT reperfusion status. Results of our current study show otherwise.

Hypothetically, a better angiographic reperfusion status could ensure a better availability of the antithrombotic agents at the microvascular level. This could reverse the effect of the "no-reflow phenomenon", which has been associated to a greater infarct growth.[5,17] However, we found no interaction of the post-EVT reperfusion status with periprocedural treatment with aspirin on the final infarct volume. We did find an interaction between post-EVT reperfusion status and periprocedural treatment with unfractionated heparin on the final infarct volume. However, in our opinion this interaction showed a biologically implausible distribution over the subgroups. If the post-EVT reperfusion status would influence the effect of periprocedural treatment with unfractionated heparin on final infarct volume, we would expect an incremental benefit or harm per increase in the post-EVT eTICI score. Therefore, we consider it probable that we found this interaction due to chance.

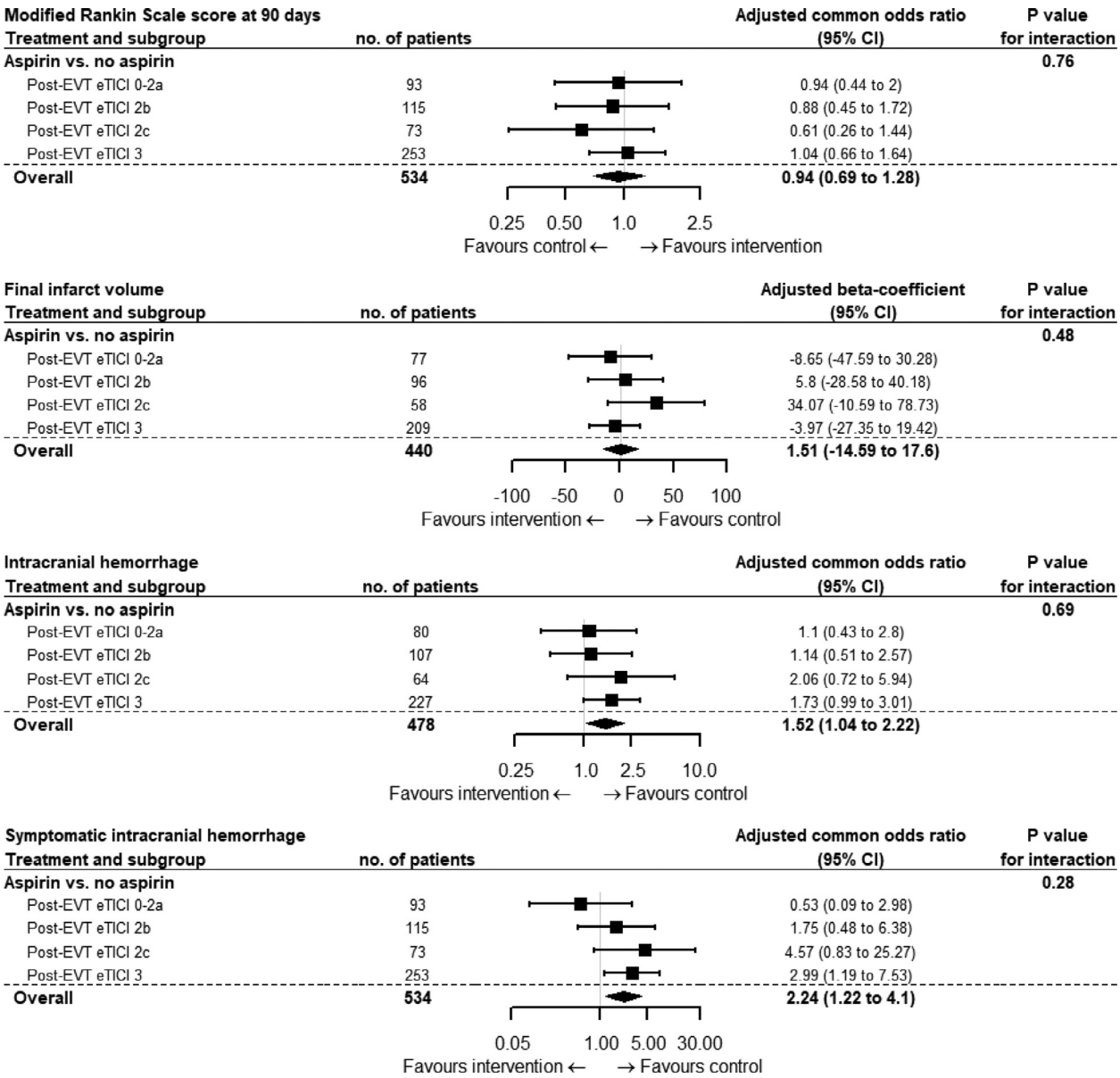

Fig. 2. *Adjusted treatment effect estimates on modified Rankin Scale score at 90 days, final infarct volume, intracranial hemorrhage, and symptomatic intracranial hemorrhage in patients allocated to aspirin versus patients allocated to no aspirin in subgroups of extended thrombolysis in cerebral infarction (eTICI) score after endovascular treatment (EVT). The presented betas reflect the effect of treatment on final infarct volume in milliliters.*

When evaluated from a safety point of view, it can also be hypothesized that a better angiographic reperfusion could further increase the risk of ICH or symptomatic ICH due to the better availability of the drug at the microvascular affected area. However, we found no interaction of the post-EVT reperfusion status with periprocedural treatment with aspirin or unfractionated heparin on ICH and symptomatic ICH occurrence. This may be explained by the fact that well-perfused tissue has a lower risk of bleeding than poorly perfused tissue.[18,19]

Overall, we also found no interaction of the post-EVT reperfusion status with periprocedural treatment with aspirin or unfractionated heparin on functional outcome after 3 months. This indicates that the post-EVT reperfusion status should not be used in the decision to give these antithrombotic agents during EVT, and that a new randomized controlled trial evaluating the safety and efficacy of these agents in patients with successful reperfusion after EVT seems not to be indicated. Currently, guidelines provide no recommendations on the periprocedural use of aspirin and unfractionated heparin during endovascular stroke treatment.[20] Before the MR CLEAN-MED trial was published, this led to a large practice variation.[15] This will have changed after publication of the trial, however, due to the results of earlier observational studies some interventionists could still consider using these agents in patients with a successful reperfusion after the procedure. The current study provides

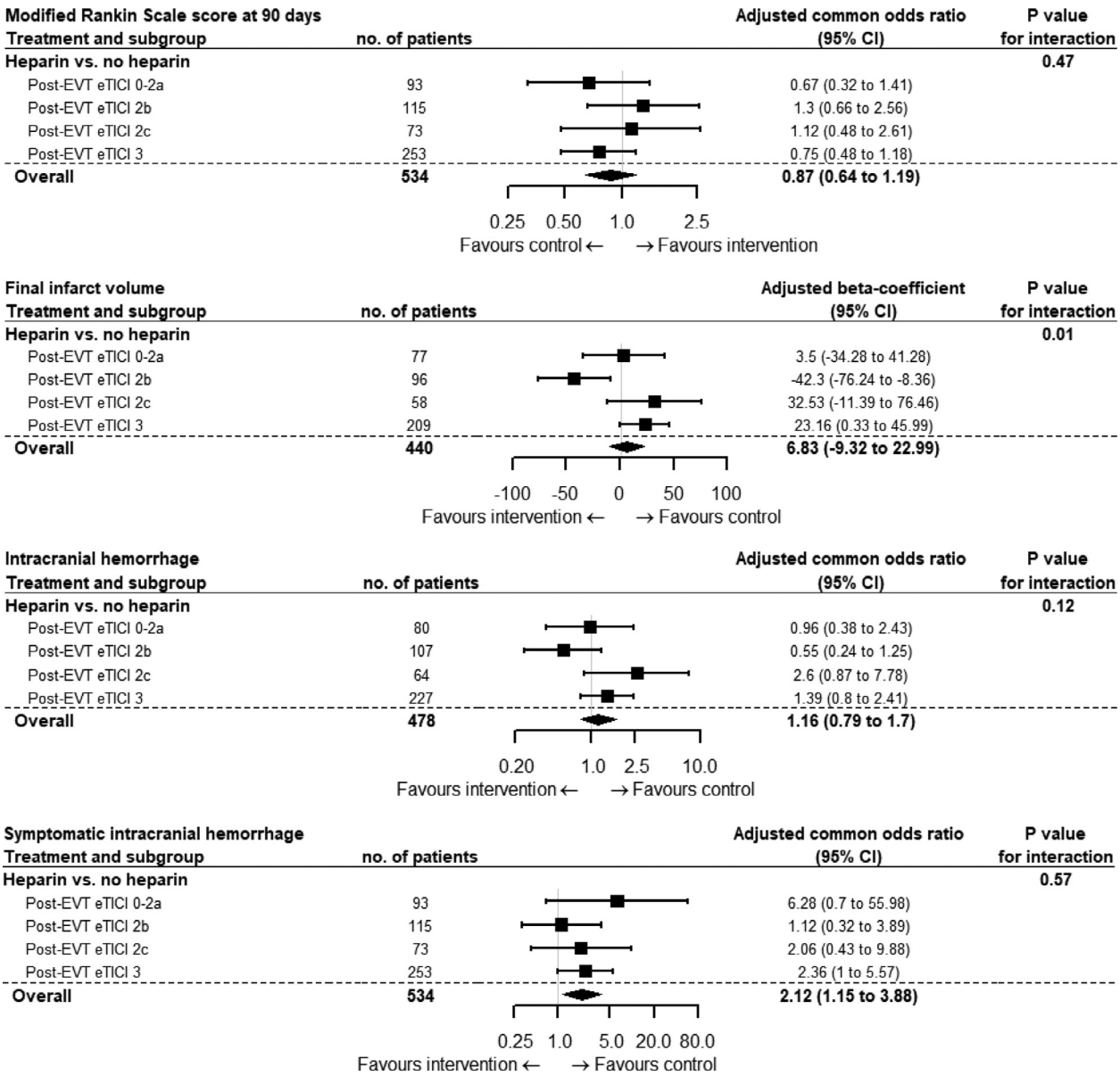

Fig. 3. *Adjusted treatment effect estimates on modified Rankin Scale score at 90 days, final infarct volume, intracranial hemorrhage, and symptomatic intracranial hemorrhage in patients allocated to unfractionated heparin versus patients allocated to no unfractionated heparin in subgroups of extended thrombolysis in cerebral infarction (eTICI) score after endovascular treatment (EVT). The presented betas reflect the effect of treatment on final infarct volume in milliliters.*

evidence that there is also no indication to administer these agents in this subgroup of patients. In general, the routine use of periprocedural aspirin or unfractionated heparin during EVT should be avoided.

The findings of this study are opposite to what the CHOICE trial demonstrated.[8] However, there were some important differences between the trials. The CHOICE trial evaluated a different type of pharmacological agent (i.e., alteplase), which was injected intra-arterially and distal to the origin of the lenticulostriate branches.[21] Local infusion warrants the use of a lower dose, which may decrease the risk of hemorrhage.[22] In addition, alteplase was administered only after successful angiographic reperfusion was achieved. This may have improved availability of the agent at the microvascular level. Although results of the CHOICE trial require replication, they are hopeful in the quest to improve microvascular reperfusion.

Limitations

Our study has limitations. First, this was a post-hoc subgroup analysis of an early-terminated randomized controlled trial with an overall neutral effect on the primary outcome. This limits the value that can be ascribed to the results.[23] However, it is the first study evaluating the interaction between periprocedural antithrombotic agents and reperfusion status after the procedure in

randomized data. Second, the inclusion and exclusion criteria used in the MR CLEAN-MED trial could limit generalizability to the overall population. In addition, patients presenting early and directly to a participating trial center without contraindications for intravenous thrombolytics were included in the parallel MR CLEAN-NOIV trial, also limiting generalizability.[24] However, criteria used in the trial were lenient and baseline characteristics suggest that the population is representative of clinical practice. Third, some patients in the MR CLEAN-MED trial did not provide deferred consent for primary outcome assessment potentially introducing selection bias. However, in the main paper of the trial, sensitivity analyses on main safety outcomes (i.e., symptomatic ICH and death from any cause) including these patients showed comparable results as main analyses. This indicates that there was no selective withdrawal of patients, limiting the risk of a bias. Last, some patients had no follow-up imaging or no follow-up imaging with good enough quality to assess ICH occurrence and final infarct volume. These patients were excluded from the secondary analyses on ICH occurrence and/or final infarct volume potentially introducing selection bias. However, a comparison of the baseline characteristics and functional outcome of these patients showed similar results as patients included in these secondary analyses. This indicates that the risk of bias in this case was also limited.

Conclusion

The overall harmful effect of periprocedural aspirin and unfractionated heparin is not different in patients with a successful reperfusion after EVT. There is no indication to start periprocedural administration of aspirin or unfractionated heparin in patients with a successful reperfusion after EVT.

Disclosures

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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.2022.106726.

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