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Safety and efficacy of aspirin, unfractionated heparin, both, or neither during endovascular stroke treatment (MR CLEAN-MED): an open-label, multicentre, randomised controlled trial

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Summary

Background Aspirin and unfractionated heparin are often used during endovascular stroke treatment to improve reperfusion and outcomes. However, the effects and risks of anti-thrombotics for this indication are unknown. We therefore aimed to assess the safety and efficacy of intravenous aspirin, unfractionated heparin, both, or neither started during endovascular treatment in patients with ischaemic stroke.

Methods We did an open-label, multicentre, randomised controlled trial with a 2×3 factorial design in 15 centres in the Netherlands. We enrolled adult patients (ie, ≥18 years) with ischaemic stroke due to an intracranial large-vessel occlusion in the anterior circulation in whom endovascular treatment could be initiated within 6 h of symptom onset. Eligible patients had a score of 2 or more on the National Institutes of Health Stroke Scale, and a CT or MRI ruling out intracranial haemorrhage. Randomisation was done using a web-based procedure with permuted blocks and stratified by centre. Patients were randomly assigned (1:1) to receive either periprocedural intravenous aspirin (300 mg bolus) or no aspirin, and randomly assigned (1:1:1) to receive moderate-dose unfractionated heparin (5000 IU bolus followed by 1250 IU/h for 6 h), low-dose unfractionated heparin (5000 IU bolus followed by 500 IU/h for 6 h), or no unfractionated heparin. The primary outcome was the score on the modified Rankin Scale at 90 days. Symptomatic intracranial haemorrhage was the main safety outcome. Analyses were based on intention to treat, and treatment effects were expressed as odds ratios (ORs) or common ORs, with adjustment for baseline prognostic factors. This trial is registered with the International Standard Randomised Controlled Trial Number, ISRCTN76741621.

Findings Between Jan 22, 2018, and Jan 27, 2021, we randomly assigned 663 patients; of whom, 628 (95%) provided deferred consent or died before consent could be asked and were included in the modified intention-to-treat population. On Feb 4, 2021, after unblinding and analysis of the data, the trial steering committee permanently stopped patient recruitment and the trial was stopped for safety concerns. The risk of symptomatic intracranial haemorrhage was higher in patients allocated to receive aspirin than in those not receiving aspirin (43 [14%] of 310 *vs* 23 [7%] of 318; adjusted OR 1·95 [95% CI 1·13–3·35]) as well as in patients allocated to receive unfractionated heparin than in those not receiving unfractionated heparin (44 [13%] of 332 *vs* 22 [7%] of 296; 1·98 [1·14–3·46]). Both aspirin (adjusted common OR 0·91 [95% CI 0·69–1·21]) and unfractionated heparin (0·81 [0·61–1·08]) led to a non-significant shift towards worse modified Rankin Scale scores.

Interpretation Periprocedural intravenous aspirin and unfractionated heparin during endovascular stroke treatment are both associated with an increased risk of symptomatic intracranial haemorrhage without evidence for a beneficial effect on functional outcome.

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Research in context

Evidence before this study

We searched PubMed for randomised controlled trials published between Jan 1, 2015, and Dec 6, 2021, using the Medical Subject Headings terms "((((antithrombotic agents OR antiplatelet agents OR platelet aggregation inhibitors OR acetylsalicylic acid OR aspirin OR agents, aspirin like OR anticoagulants OR heparin OR unfractionated heparin) AND (acute stroke OR brain ischemia OR brain infarction OR intracranial embolism) AND (ischemic stroke OR ischaemic stroke) AND (endovascular procedure OR Thrombectomy OR Thrombectomies OR embolectomy))))" with no language restrictions. We identified no published randomised clinical trials on periprocedural antithrombotic agents during endovascular stroke treatment. The use of antiplatelet medication in ischaemic stroke in general has a small beneficial effect. In the ARTIS study, early administration of intravenous aspirin after treatment with intravenous thrombolytics was associated with an increased risk of intracranial haemorrhage, but did not alter functional outcome. This study was reported before the widespread introduction of endovascular therapy, and the 4·3% risk of symptomatic intracranial haemorrhage, even in the intervention group of the study, was low. Several observational studies suggested beneficial effects of antiplatelets in patients treated with endovascular stroke therapy, with moderately increased risks of intracranial haemorrhage. The International Stroke Trial showed no net effect of heparin treatment for patients with ischaemic stroke in general. In the MR CLEAN Registry, there was no significant difference in functional outcome between patients treated with intravenous heparin during endovascular therapy and those who were not, but centres using heparin more often had better outcomes. Other observational studies have reported a slight increase in symptomatic intracranial haemorrhage with heparin treatment, but have also suggested a beneficial effect on functional outcome. Due to a lack of data from randomised controlled trials, large practice variation exists.

Added value of this study

We report the first randomised controlled trial evaluating the safety and efficacy of periprocedural use of aspirin or unfractionated heparin during endovascular treatment of acute ischaemic stroke. Our data show that the evaluated dosages of the anti-thrombotic agents are associated with an increased risk of symptomatic intracranial haemorrhage without evidence for a beneficial effect on functional outcome.

Implications of all the available evidence

The results of our trial suggest that avoiding routine periprocedural treatment with aspirin or unfractionated heparin might increase chances of recovery after endovascular stroke treatment. In addition, the safety and efficacy of using anti-thrombotic agents during endovascular stroke therapy for other indications (eg, acute carotid stenting) should be further evaluated.

Introduction

After endovascular treatment for ischaemic stroke, due to an intracranial large-vessel occlusion in the anterior circulation, many patients do not recover despite fast and successful angiographic reperfusion.[1,2] Periprocedural anti-thrombotics might enhance angiographic and microvascular reperfusion, and are often used to reduce thrombotic complications.[3,4] However, for aspirin and heparin, the potential benefits are not known on whether its periprocedural use outweigh the potentially increased risk of symptomatic intracranial haemorrhage.[3,5]

Guidelines advise against the early administration of aspirin after treatment with intravenous thrombolytics because of its increased risk of symptomatic intracranial haemorrhage without evidence for a beneficial effect in a previous trial.[6,7] However, this trial was done in patients with ischaemic stroke treated with intravenous thrombolytics before the introduction of endovascular treatment, and the 4·3% risk of symptomatic intracranial haemorrhage in the intervention group was low.[8] Guidelines provide no recommendations on the early administration of heparin. Two observational studies found that periprocedural use of heparin was associated with good clinical outcomes and low risks of intracranial haemorrhage.[9,10] No randomised trials on treatment with periprocedural anti-thrombotics in patients treated with endovascular treatment have been done. Therefore, guidelines provide no recommendations on the periprocedural administration of anti-thrombotics and, consequently, large practice variation exists.[4,6,11]

In the current study—the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN-MED)—we aimed to assess the safety and efficacy of intravenous aspirin, unfractionated heparin, both, or neither started during endovascular treatment in patients with ischaemic stroke due to an intracranial large-vessel occlusion in the anterior circulation.

Methods

Study design and participants

We did an open-label, multicentre, randomised controlled trial with a blinded outcome assessment and a 2×3 factorial design in 15 centres in the Netherlands. We included adult patients (ie, ≥18 years) with ischaemic stroke due to an intracranial large-vessel occlusion in the anterior circulation (ie, the intracranial part of the internal carotid artery or the middle cerebral artery segment M1 or proximal M2) in whom endovascular treatment could be initiated within 6 h from symptom onset or last seen well. Eligible patients had a score of

2 or more on the National Institutes of Health Stroke Scale (NIHSS), and a CT or MRI ruling out intracranial haemorrhage. Patients with pre-stroke disability (ie, a modified Rankin Scale score >2), treatment with intravenous thrombolytics despite a contraindication for its use, contraindications for aspirin or unfractionated heparin, use of heparin in a therapeutic (non-prophylactic) dosage, value on the international normalised ratio (INR) test exceeding 3·0, or known haemorrhagic diathesis or thrombocytopenia (<90×10^9 cells per L) were excluded. Detailed inclusion and exclusion criteria are listed in the study protocol. Patients with previous use of anti-thrombotics (other than heparin in a therapeutic dosage or vitamin K antagonists with an INR >3·0) and treatment with intravenous thrombolytics according to standard protocol were not excluded. We did not keep a record of patients who were screened for eligibility.

The study protocol was approved by a central medical ethics committee at Erasmus University Medical Center.[12] All centres used a deferred consent procedure in accordance with national legislation.[13] All patients or their legal representatives provided written deferred consent after randomisation and study treatment. If no deferred consent was given, only the following characteristics were collected for a strictly anonymised safety registry: study number, treatment allocation, in-hospital symptomatic intracranial haemorrhage, and in-hospital death. The anonymised safety registry included all patients randomly assigned to the treatment groups irrespective of whether a patient had provided written deferred consent. If patients died before deferred consent could be obtained, all collected data were used.

Randomisation and masking

Treating physicians or local investigators randomly assigned eligible patients by means of a web-based procedure in which randomisation was done using permuted blocks and was stratified by centre. Block sizes varied from 4×6 to 10×6. After stopping allocation to moderate-dose unfractionated heparin, block sizes varied from 4×4 to 10×4. Patients were randomly assigned (1:1) to receive either intravenous aspirin or no aspirin, and randomly assigned (1:1:1) to receive moderate-dose unfractionated heparin, low-dose unfractionated heparin, or no unfractionated heparin. Local investigators and treating physicians were aware of treatment allocation. Clinical outcomes were collected by trained research nurses unaware of treatment allocation. Independent committees were masked to treatment allocation and adjudicated serious adverse event reports and primary outcome data based on the interview reports. Imaging outcomes were assessed with standardised case report forms by an imaging committee masked to all clinical data except for the anatomical location of the stroke (ie, the left or right cerebral hemisphere).

Procedures

Study treatment consisted of intravenous aspirin (300 mg bolus) or no aspirin and of moderate-dose unfractionated heparin (5000 IU bolus followed by 1250 IU/h for 6 h), low-dose unfractionated heparin (5000 IU bolus followed by 500 IU/h for 6 h), or no unfractionated heparin. All study treatments were started directly after a 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—ie, before closure of the groin puncture site. In case an untoward event occurred (eg, perforation or haemorrhage), the decision to stop the study medication was left to the discretion of the treating physician.

We used intravenous aspirin, as opposed to oral treatment, as it can be administered independent of patient status (eg, swallowing problems or reduced level of consciousness). All patients underwent neurological assessments by certified assessors at baseline, 24 h, and at 5–7 days or at hospital discharge. Patients underwent non-contrast brain CT and CT angiography at baseline as part of usual care. Follow-up imaging could be done with either brain CT or MRI. Patients who were followed-up with CT underwent non-contrast CT and CT angiography between 12 h and 36 h after randomisation and another non-contrast CT at 5–7 days or at hospital discharge. Patients who were followed-up with MRI underwent MRI and MR angiography between 12 h and 36 h after randomisation. No additional imaging at 5–7 days or discharge was required. The choice of modality was left to the participating centres. However, participating centres had to adhere to the same follow-up imaging modality during the trial to prevent bias. All patients were followed-up until the final assessment at 90 days. Clinical outcome data at 90 days were collected centrally through standardised telephone interviews. If the included patient could not be interviewed (eg, because of dysphasia), a legal representative was interviewed.

Outcomes

The primary outcome was the score on the modified Rankin Scale (0 [no symptoms] to 6 [death]) at 90 days. Secondary outcomes were the NIHSS score (0 [no deficit] to 42 [maximum deficits]) at 24 h and at 5–7 days or at hospital discharge; reperfusion measured with the extended treatment in cerebral ischaemia score (eTICI; 0 [no reperfusion] to 3 [complete reperfusion]) on final angiography of endovascular treatment, expressed as successful (eTICI score ≥2B) and excellent (eTICI score ≥2C) reperfusion; complete recanalisation measured with the modified arterial occlusive lesion score (0 [no recanalisation] to 3 [complete recanalisation]) on CT angiography or MR angiography at 24 h; final infarct volume assessed with non-contrast CT at 5–7 days or with MRI at 24 h; scores on the EuroQol Group

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5-Dimension Self-Report Questionnaire (–0·329 to 1; higher scores indicate better quality of life) and Barthel index (0–100; higher scores indicate less interference with daily activities) at 90 days; and all possible dichotomisations of the modified Rankin Scale at 90 days.

Safety outcomes were any intracranial haemorrhage and symptomatic intracranial haemorrhage according to the Heidelberg Bleeding Classification; extracranial haemorrhage requiring transfusion or resulting in death; embolisation in a new territory during endovascular treatment; infarction in a new territory on non-contrast CT on day 5–7 or MRI at 24 h; and death from all causes within 90 days.[14]

Statistical analysis

For the **statistical analysis plan** see https://www.mrclean-med.nl/

We followed the statistical analysis plan, which is available online. For aspirin, we assumed an absolute 5% increase in the proportion of patients with a modified Rankin Scale score of 0–2 at 90 days. We estimated that a study size of 1500 participants would be sufficient to provide a power of 84% to detect a significant treatment effect based on this assumption. Assuming the same treatment effect of unfractionated heparin, the estimated power to detect this effect was 78%. Estimated power was lower as we randomly assigned two-thirds of patients to receive unfractionated heparin (low dose or moderate dose) versus one-third to no unfractionated heparin. Underlying assumptions are described in the study protocol.[12] The main analyses consisted of the comparison between patients allocated to aspirin versus no aspirin, and to unfractionated heparin versus no unfractionated heparin. Additionally, we compared the different dosages (ie, moderate dose or low dose) of unfractionated heparin versus no unfractionated heparin. We tested for a possible interaction between the effect of aspirin and of unfractionated heparin on the modified Rankin Scale score and symptomatic intracranial haemorrhage. The main effect analyses were done in the modified intention-to-treat population, consisting of all patients for whom consent was obtained. The data from the safety registry were used for a sensitivity analysis of the treatment effect estimates of aspirin and unfractionated heparin on symptomatic intracranial haemorrhage and death.

See **Online** for appendix

The primary effect parameter is reported as the shift on the modified Rankin Scale, quantified with the common odds ratio (OR), estimated with ordinal logistic regression. Secondary effect parameters and safety parameters were estimated using linear or logistic regression analyses as appropriate. For primary and secondary effect parameters a common OR of less than 1 indicates a decreased risk of good outcome—ie, a poor effect of the intervention. For safety parameters, this point estimate is the other way around—ie, an OR of more than 1 indicates an increased risk of a poor outcome or a poor effect of the intervention. All treatment effect analyses were adjusted for the following baseline prognostic variables: age, pre-stroke modified Rankin Scale score, time from onset to door of endovascular treatment centre, time from door of endovascular treatment centre to groin puncture, NIHSS score, and collateral score. We report adjusted and unadjusted estimates with corresponding 95% CIs.

Prespecified subgroup analyses were done by testing for subgroup effect between the specific baseline characteristic and treatment. The effect of intervention on the modified Rankin Scale was analysed for tertiles of age; sex; tertiles of systolic blood pressure; tertiles of NIHSS score; tertiles of time from stroke onset to randomisation, groin puncture, and revascularisation; diabetes mellitus; atrial fibrillation; extracranial carotid occlusion; occlusion location; Alberta Stroke Programme Early CT Score; collateral score; type of device; treatment with intravenous thrombolytics; and previous use of anti-thrombotics (ie, antiplatelet agents, vitamin K antagonists, or direct oral anticoagulants). In an explorative post-hoc analysis, the effect of intervention on the occurrence of symptomatic intracranial haemorrhage was analysed for the same subgroups. To limit the risks of false-positive findings in the subgroup analyses, we considered a subgroup effect with a p value of less than 0·001 as statistically significant and clinically relevant.

An independent, unblinded trial statistician did the interim analyses after every 300 included patients, and safety analyses after every five symptomatic intracranial haemorrhages or ten deaths. After the seventh safety analysis, this analysis was extended to every ten symptomatic intracranial haemorrhages or 20 deaths. An independent and unblinded data safety and monitoring board evaluated these analyses. Detailed descriptions and data for the interim and safety analyses are provided in the appendix (p 6).

For regression analyses, we assigned the worst score for all unassessed clinical outcome measures for patients who died within the study period. All other missing values were replaced with multiple imputation (n=5 imputation sets). We did all statistical analyses using R (version 4.0.5). This trial is registered with the International Standard Randomised Controlled Trial Number, ISRCTN76741621.

Trial termination

On April 16, 2019, the data safety and monitoring board reviewed the fourth safety analysis of the trial. Following this analysis, the data safety and monitoring board advised the trial steering committee to stop assigning moderate-dose unfractionated heparin to new study participants because of a safety concern. No safety concerns related to the other study treatments were noted. The trial steering committee followed the advice

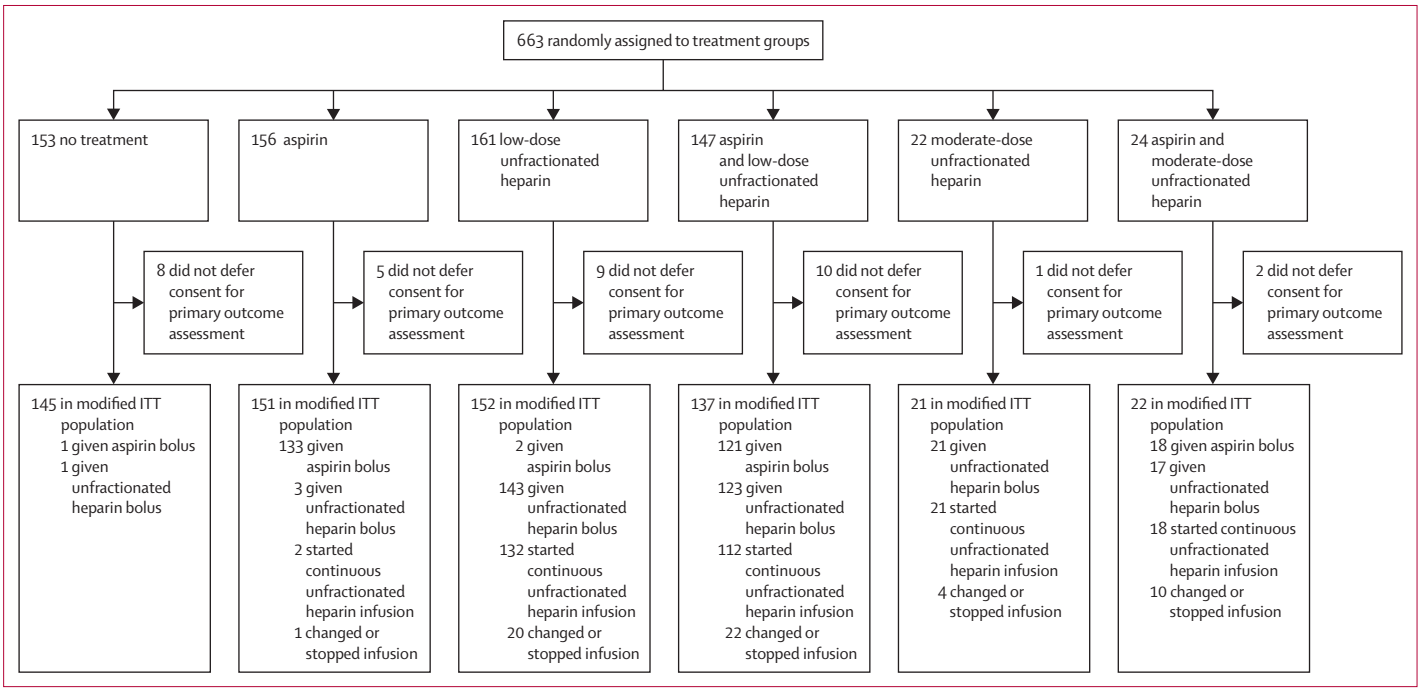

Figure 1: **Treatment allocations in the safety registry and modified ITT population**
ITT=intention-to-treat.

of the data safety and monitoring board and was unblinded to the allocation of moderate-dose heparin, but not to the other treatment allocations. On Jan 27, 2021, the data safety and monitoring board reviewed the eleventh safety analysis and recommended halting inclusion and unblinding of the trial steering committee because of safety concerns with the study treatments for which enrolment was ongoing. On Feb 4, 2021, after unblinding and analysis of the data, the trial steering committee permanently stopped patient recruitment. No patients were enrolled after the advice of the data safety and monitoring board was obtained. The follow-up of patients already enrolled in the trial, but not yet at their 90-day follow-up, was finished before closure of the database.

To adjust for the early stopping of moderate-dose unfractionated heparin, we included a term for time of randomisation (ie, before versus after stopping allocation of patients to moderate-dose unfractionated heparin) in the regression models of the main analyses. For the comparison of moderate-dose unfractionated heparin with no unfractionated heparin, we only evaluated patients who were randomly assigned to the treatment group before stopping the allocation of moderate-dose unfractionated heparin.

Role of the funding source

The funders of the study had no role in study design, planning, data analysis, data interpretation, or writing of the report.

Results

Between Jan 22, 2018, and Jan 27, 2021, we randomly assigned 663 patients; of whom, 628 (95%) provided deferred consent or died before consent could be asked and were included in the modified intention-to-treat population (figure 1). Of the 628 included patients, 310 (49%) were allocated to receive aspirin and 318 (51%) to not receive aspirin, and 332 (53%) were allocated to receive unfractionated heparin (289 [87%] with low-dose unfractionated heparin and 43 [13%] with moderate-dose unfractionated heparin) and 296 (47%) to receive no unfractionated heparin. Of the 305 patients who were allocated to receive aspirin and had complete data, 272 (89%) received a bolus of aspirin. 304 (92%) of 332 patients allocated to receive unfractionated heparin received a bolus of unfractionated heparin and 283 (90%) of 315 patients who were allocated to receive unfractionated heparin and had complete data received a continuous infusion of unfractionated heparin. The median time from groin puncture to bolus administration of aspirin was 5 min (IQR 0–12), and the median time from groin puncture to bolus administration of unfractionated heparin was 6 min (0–13). No patients in the modified intention-to-treat population were lost to follow-up.

The median age of patients in the study population was 73 years (IQR 65–81). 332 (53%) of 628 patients were men and 296 (47%) were women. 498 (79%) of 628 patients were transferred from a primary hospital; the median baseline NIHSS score was 15 (IQR 9–19)

	Aspirin (n=310)	No aspirin (n=318)	Unfractionated heparin (n=332)	No unfractionated heparin (n=296)
Age, years	73 (66–82)	73 (64–81)	74 (66–82)	73 (64–81)
Sex				
Male	154 (50%)	178 (56%)	179 (54%)	153 (52%)
Female	156 (50%)	140 (44%)	153 (46%)	143 (48%)
Transferred from primary hospital	245 (79%)	253 (80%)	256 (77%)	242 (82%)
NIHSS score*	15 (9–19)	15 (9–19)	16 (10–19)	14 (8–19)
History of atrial fibrillation	77 (25%)	79 (25%)	81 (24%)	75 (25%)
History of hypertension	138 (45%)	151 (47%)	152 (46%)	137 (46%)
Previous ischaemic stroke	58 (19%)	57 (18%)	61 (18%)	54 (18%)
Pre-stroke modified Rankin Scale score†				
0	200 (65%)	220 (69%)	219 (66%)	201 (68%)
1	58 (19%)	56 (18%)	64 (19%)	50 (17%)
2	33 (11%)	27 (8%)	31 (9%)	29 (10%)
≥3	14 (5%)	12 (4%)	14 (4%)	12 (4%)
Treatment with intravenous thrombolytics	229 (74%)	237 (75%)	246 (74%)	220 (74%)
Time from stroke onset to intravenous thrombolytics (min)	78 (60–111)	80 (60–127)	80 (60–124)	78 (60–119)
ASPECTS‡	9 (8–10)	9 (8–10)	9 (8–10)	9 (8–10)
Occlusion side				
Right hemisphere	149 (48%)	160 (50%)	165 (50%)	144 (49%)
Left hemisphere	161 (52%)	158 (50%)	167 (50%)	152 (51%)
Occluded segment				
Infraclinoid internal carotid artery	60 (19%)	69 (22%)	74 (22%)	55 (19%)
Supraclinoid internal carotid artery	18 (6%)	19 (6%)	21 (6%)	16 (5%)
Middle cerebral artery M1 segment	144 (47%)	164 (52%)	162 (49%)	146 (49%)
Middle cerebral artery M2 segment	83 (27%)	64 (20%)	72 (22%)	75 (25%)
Other§	4 (1%)	2 (1%)	2 (1%)	4 (1%)
Extracranial internal carotid artery occlusion	55 (18%)	44 (14%)	53 (16%)	46 (16%)
Poor collateral score (<50%)	109 (35%)	105 (33%)	122 (37%)	92 (31%)
Time from stroke onset to door of endovascular therapy centre, min	143 (105–195)	143 (110–197)	140 (103–200)	146 (110–195)
Time from door of endovascular therapy centre to groin puncture, min	33 (23–51)	31 (22–48)	35 (25–54)	30 (21–45)

Data are median (IQR) or n (%). NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT score. *NIHSS scores range from 0 to 42, with higher scores indicating more severe neurological deficits. Scores for 21 (3%) of 628 patients were missing or incomplete. †Scores on the modified Rankin Scale of functional disability range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence. Pre-stroke modified Rankin Scale scores were missing for eight (1%) of 628 patients. ‡The ASPECTS is a measure of the extent of early ischaemic changes on non-contrast CT. Scores range from 0 to 10, with higher scores indicating fewer early ischaemic changes. Scores for three (1%) of 628 patients were missing. §Anterior cerebral artery A1 or A2 segment, or none.

Table 1: **Baseline characteristics and process measures of the modified intention-to-treat population**

and the median onset to groin puncture time was 175 min (144–228; table 1). Of the 628 patients, 538 (86%) had thrombectomy, 59 (9%) had only digital subtraction angiography, 12 (2%) had only catheterisation, and 16 (3%) had no endovascular procedure done. Acute carotid stenting was done in 30 (5%) of 628 patients, and percuta-neous transluminal angioplasty in 43 (7%) patients. Information about non-trial anti-thrombotics given during endovascular procedure for patients treated with percutaneous transluminal angioplasty or acute carotid stenting is shown in the appendix (p 7). The median duration of performed procedure was 46 min (IQR 30–70). More comprehensive data for medical history and previous drug use are summarised in the appendix (p 8).

Patients allocated to receive aspirin (adjusted common OR 0·91 [95% CI 0·69–1·21]) had worse but not significantly different modified Rankin Scale distributions than those who did not receive aspirin; and those allocated to unfractionated heparin (0·81 [0·61–1·08]) also had worse but not significantly different distributions than those who did not receive unfractionated heparin (figure 2; table 2). The unfavourable shift in the modified Rankin Scale distribution at 90 days after randomisation was significant for moderate-dose unfractionated heparin (adjusted common OR 0·42 [95% CI 0·18–0·99]) but not for low-dose unfractionated heparin (0·86 [0·64–1·16]) compared with those who did not receive unfractionated heparin (appendix pp 9, 16). We found no interaction between aspirin and unfractionated heparin on the effect of the primary outcome (p=0·77).

Patients allocated to unfractionated heparin more often had complete recanalisation after 24 h than those not allocated to unfractionated heparin (adjusted OR 1·89 [95% CI 1·16–3·09]; table 2). No significant differences were observed for the other secondary outcomes. Outcomes for each treatment group and unadjusted treatment effect estimates are given in the appendix (pp 10–11).

Symptomatic intracranial haemorrhage occurred more often in patients allocated to receive aspirin than in those not receiving aspirin (43 [14%] of 310 *vs* 23 [7%] of 318; adjusted OR 1·95 [95% CI 1·13–3·35]), as well as in patients allocated to receive unfractionated heparin than in those not receiving unfractionated heparin (44 [13%] of 332 *vs* 22 [7%] of 296; 1·98 [1·14–3·46]; table 3). This finding was accompanied by a non-significant increase in deaths for both aspirin (adjusted OR 1·11 [95% CI 0·73–1·69]) and unfractionated heparin (1·26 [0·82–1·92]). No interaction between aspirin and unfractionated heparin on the effect of symptomatic intracranial haemorrhage was observed (p=0·61). Sensitivity analyses in the safety registry showed comparable results (appendix p 12). In patients allocated to low-dose unfractionated heparin, we observed a non-significant increase in the rates of symptomatic intracranial haemorrhage (adjusted OR 1·76 [95% CI 0·98–3·18]) and death (1·05 [0·68–1·65]). Patients allocated to moderate-dose unfractionated heparin had a significantly increased risk of symptomatic intracranial haemorrhage (adjusted OR 6·04 [95% CI 1·31–27·7]) and death (5·85 [1·70–20·2]). We observed no significant differences for the other safety outcomes (table 3). Safety outcomes for each treatment group are shown in the appendix (p 13).

In the subgroup analyses, the point estimate of the treatment effect of unfractionated heparin on functional outcome was beneficial in patients with an onset to recanalisation time of less than 195 min and harmful in patients with longer onset to recanalisation times (p=0·0002; appendix p 17). We observed no other clinically relevant differences in treatment effects in the subgroup analyses (appendix pp 18–20). Explorative primary outcome and primary safety outcomes of patients treated with intravenous thrombolytics and of patients treated with percutaneous transluminal angioplasty or acute carotid stenting are shown in the appendix (pp 7, 14).

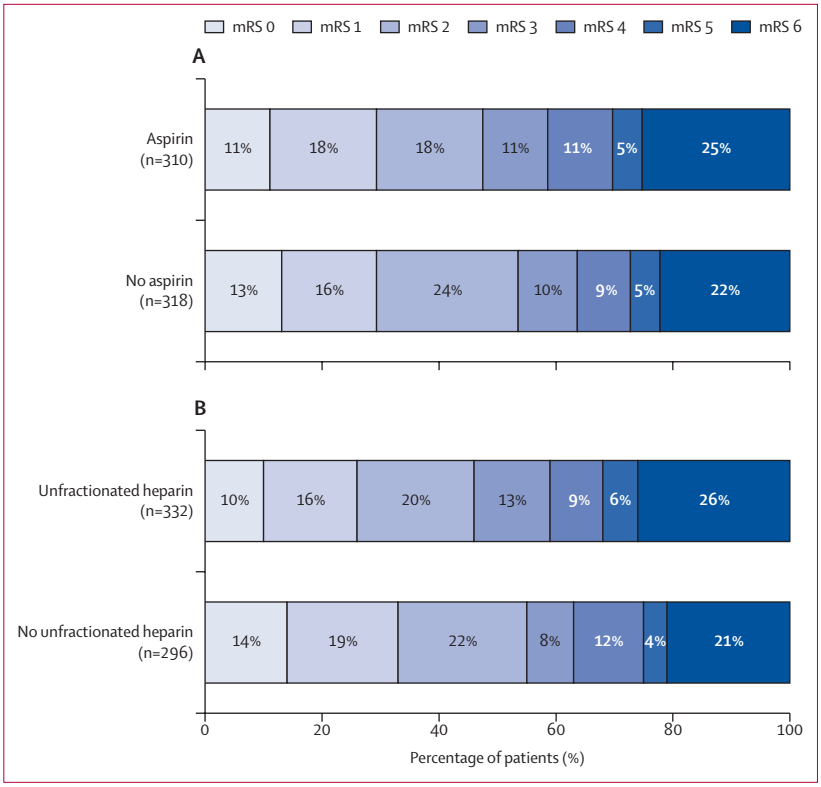

Figure 2: **Distribution of mRS scores at 90 days**
(A) Patients allocated to aspirin versus patients allocated to no aspirin. (B) Patients allocated to unfractionated heparin versus patients allocated to no unfractionated heparin. A non-significant shift towards worse functional outcomes was observed for both allocation to aspirin versus allocation to no aspirin (adjusted common odds ratio 0·91 [95% CI 0·69–1·21]) and for allocation to unfractionated heparin versus allocation to no unfractionated heparin (0·81 [0·61–1·08]). mRS=modified Rankin Scale.

Discussion

In this randomised controlled trial that was stopped early for concerns of safety, we found that periprocedural administration of aspirin or unfractionated heparin in patients with ischaemic stroke treated with endovascular treatment was associated with an increased risk of symptomatic intracranial haemorrhage. We also found no evidence for a beneficial effect on functional outcome of either treatment.

The results of several observational studies that assessed the effects of periprocedural use of antiplatelets during endovascular treatment pointed towards a beneficial effect on functional outcome.[3,4,15] Their antithrombotic effect can reduce thrombotic complications and prevent distal platelet-fibrin occlusive lesions compromising microvascular reperfusion.[16,17] However, our trial showed that periprocedural aspirin increases the risk of symptomatic intracranial haemorrhage and should not be routinely administered during endovascular treatment.

Systemic heparinisation is often used by interventionists to reduce thrombotic complications during endovascular procedures for a variety of indications.[11,18,19] In addition, unfractionated heparin can dissolve neutrophil extracellular traps.[20] Neutrophil extracellular traps can cause incomplete microvascular reperfusion by trapping platelets and increasing fibrin deposition.[20,21] Observational studies found that unfractionated heparin might improve functional outcomes in patients with ischaemic stroke treated with endovascular treatment.[3,5,11] In our trial, we did find higher recanalisation rates in the unfractionated heparin group. However, this benefit

	Aspirin (n=310)	No aspirin (n=318)	Effect estimates			Unfractionated heparin (n=332)	No unfractionated heparin (n=296)	Effect estimates		
			Common OR (95% CI)	OR (95% CI)	β-coefficient (95% CI)			Common OR (95% CI)	OR (95% CI)	β-coefficient (95% CI)
Primary outcome										
Modified Rankin Scale score at 90 days	3 (1 to 6)	2 (1 to 5)	0·91 (0·69 to 1·21)	..	..	3 (1 to 6)	2 (1 to 4)	0·81 (0·61 to 1·08)	..	..
Secondary outcomes										
Modified Rankin Scale score of 0–1 at 90 days	90 (29%)	93 (29%)	..	1·01 (0·69 to 1·46)	..	86 (26%)	97 (33%)	..	0·82 (0·56 to 1·19)	..
Modified Rankin Scale score of 0–2 at 90 days	146 (47%)	170 (53%)	..	0·77 (0·53 to 1·10)	..	154 (46%)	162 (55%)	..	0·78 (0·54 to 1·13)	..
Modified Rankin Scale score of 0–3 at 90 days	181 (58%)	203 (64%)	..	0·83 (0·57 to 1·20)	..	197 (59%)	187 (63%)	..	0·96 (0·66 to 1·40)	..
Modified Rankin Scale score of 0–4 at 90 days	215 (69%)	233 (73%)	..	0·90 (0·61 to 1·35)	..	226 (68%)	222 (75%)	..	0·74 (0·49 to 1·11)	..
NIHSS score at 24 h†	6 (2 to 14)	6 (1 to 13)	..	..	0·65 (−1·03 to 2·33)	7 (2 to 14)	5 (1 to 12)	..	..	1·60 (−0·11 to 3·30)
NIHSS score at 5–7 days or discharge†	2 (0 to 8)	3 (0 to 7)	..	..	1·24 (−0·83 to 3·31)	3 (1 to 9)	2 (0 to 7)	..	..	1·91 (−0·17 to 3·98)
EQ-5D-5L score at 90 days‡	0·7 (0·0 to 0·9)	0·7 (0·1 to 0·9)	..	..	−0·02 (−0·08 to 0·03)	0·7 (0·0 to 0·9)	0·7 (0·1 to 0·9)	..	..	−0·03 (−0·08 to 0·03)
Barthel Index at 90 days§	100 (80 to 100)	100 (85 to 100)	..	..	−3·70 (−9·58 to 2·18)	100 (85 to 100)	100 (85 to 100)	..	..	−2·28 (−8·18 to 3·62)
eTICI score ≥2b on final angiography of endovascular therapy¶	238/290 (82%)	231/294 (79%)	..	1·22 (0·80 to 1·84)	..	252/312 (81%)	217/272 (80%)	..	0·93 (0·61 to 1·42)	..
eTICI score ≥2c on final angiography of endovascular therapy¶	173/290 (60%)	176/294 (60%)	..	1·00 (0·72 to 1·39)	..	184/312 (59%)	165/272 (61%)	..	0·85 (0·61 to 1·20)	..
Complete recanalisation (mAOL of 3) at 24 h CT or MR angiography‖	191/220 (87%)	208/245 (85%)	..	1·02 (0·65 to 1·62)	..	217/243 (89%)	182/222 (82%)	..	1·89 (1·16 to 3·09)	..
Final infarct volume on non-contrast CT or MRI, mL**	24 (4·3 to 81)	24 (5·1 to 78)	..	..	2·98 (−11·2 to 17·2)	27 (6·3 to 92)	20 (3·3 to 64)	..	..	10·2 (−3·97 to 24·3)

Data are median (IQR), n (%), or n/N (%), unless otherwise specified. OR=odds ratio. NIHSS=National Institutes of Health Stroke Scale. EQ-5D-5L=the 5 level EuroQol Group 5-Dimension Self-Report. eTICI=extended Thrombolysis in Cerebral Infarction. mAO=modified Arterial Occlusive Lesion. *Treatment effects were adjusted for age, pre-stroke modified Rankin Scale score, NIHSS at baseline, collateral score at baseline, time from onset to door of intervention hospital, time from door intervention hospital to groin puncture, and inclusion before or after stopping the allocation of moderate-dose unfractionated heparin. †The NIHSS score was determined for survivors only. The score at 24 h was not available for 48 patients: 38 (79%) died before assessment was done and ten (21%) had incomplete or missing scores. The score at 5–7 days or discharge was not available for 101 patients: 82 (81%) died before assessment was finished and 19 (19%) had incomplete or missing scores. ‡EQ-5D-5L scores range from −0·329 to 1, with higher scores indicating a better quality of life. §Barthel Index scores range from 0 to 100, with 0 indicating severe disability, and 95 to 100 indicating no disability that interferes with daily activities. ¶eTICI scores range from grade 0 to grade 3, with grade 0 indicating 0% reperfusion of macrovascular vessels on digital subtraction angiography, and grade 3 indicating 100% reperfusion. Grade 2 is subdivided as 2a (1–49% reperfusion), 2b (50–89% reperfusion), and 2c (90–99% reperfusion). ‖mAOL scores range from 0 to 3, with 0 indicating no recanalisation, and 3 indicating complete recanalisation with any distal flow. The score was not available for 163 patients. **Data for final infarct volume on non-contrast CT or MRI were not available for 123 patients.

Table 2: **Primary and secondary outcomes and adjusted* treatment effects in the modified intention-to-treat population**

	Aspirin (n=310)	No aspirin (n=318)	Odds ratio (95% CI)		Unfractionated heparin (n=332)	No unfractionated heparin (n=296)	Odds ratio (95% CI)	
			Unadjusted	Adjusted*			Unadjusted	Adjusted*
Safety outcomes†								
Intracranial haemorrhage	134/272 (49%)	120/281 (43%)	1·25 (0·91–1·72)	1·26 (0·90–1·76)	147/298 (49%)	107/255 (42%)	1·35 (0·95–1·93)	1·27 (0·87–1·84)
Symptomatic intracranial haemorrhage	43 (14%)	23 (7%)	2·07 (1·21–3·52)	1·95 (1·13–3·35)	44 (13%)	22 (7%)	1·90 (1·11–3·26)	1·98 (1·14–3·46)
Extracranial haemorrhage	9 (3%)	13 (4%)	0·70 (0·30–1·67)	0·70 (0·29–1·70)	11 (3%)	11 (4%)	0·89 (0·38–2·08)	0·90 (0·37–2·17)
Embolisation in new territory during endovascular treatment	38 (12%)	37 (12%)	1·06 (0·65–1·72)	1·05 (0·64–1·71)	43 (13%)	32 (11%)	1·23 (0·75–2·00)	1·10 (0·67–1·83)
Infarction in new territory on MRI at 24 h or on non-contrast CT at 5–7 days	76/153 (50%)	86/165 (52%)	0·80 (0·55–1·16)	0·80 (0·55–1·16)	71/154 (46%)	91/164 (55%)	0·78 (0·54–1·14)	0·75 (0·51–1·10)
Death from any cause	79 (25%)	69 (22%)	1·23 (0·85–1·79)	1·11 (0·73–1·69)	86 (26%)	62 (21%)	1·32 (0·91–1·91)	1·26 (0·82–1·92)
Other serious adverse events†								
Stroke progression	32 (10%)	34 (11%)	NT	NT	37 (11%)	29 (10%)	NT	NT
New ischaemic stroke	8 (3%)	18 (6%)	NT	NT	10 (3%)	16 (5%)	NT	NT
Cardiac ischaemia	2 (1%)	6 (2%)	NT	NT	4 (1%)	4 (1%)	NT	NT
Allergic reaction	3 (1%)	1 (<1%)	NT	NT	1 (<1%)	3 (1%)	NT	NT
Pneumonia	57 (18%)	38 (12%)	NT	NT	48 (14%)	47 (16%)	NT	NT
Other infection	37 (12%)	41 (13%)	NT	NT	44 (13%)	34 (11%)	NT	NT
Other serious adverse event	46 (15%)	54 (17%)	NT	NT	57 (17%)	43 (15%)	NT	NT
Any serious adverse event	158 (51%)	160 (50%)	NT	NT	181 (55%)	137 (46%)	NT	NT

Data are n (%) or n/N (%), unless otherwise specified. NIHSS=National Institutes of Health Stroke Scale. NT=not tested, as this test was not specified in the statistical analysis plan. *Values were adjusted for age, pre-stroke modified Rankin Scale score, NIHSS at baseline, collateral score at baseline, time from onset to door of intervention hospital, time from door intervention hospital to groin puncture, and inclusion before or after early termination of moderate-dose unfractionated heparin arms. †Only first events of a type are listed. Patients having multiple events of one type were counted once.

Table 3: **Safety outcomes with treatment effects and occurrence of other serious adverse events in the modified intention-to-treat population**

did not outweigh the increased risk of symptomatic intracranial haemorrhage. The evaluated dosages of unfractionated heparin should be avoided as part of routine treatment.

Subgroup analyses suggest that patients with shorter treatment delays might have less harm from heparin. Similar to other acute stroke therapies, the effects of heparin might be time dependent.[22,23] However, subgroup effects in a trial with a neutral overall treatment effect on the primary outcome should be interpreted with caution because of the risk of false-positive findings.[24]

Periprocedural anti-thrombotic agents are also administered during endovascular stroke therapy for more specific indications such as acute carotid stenting.[25] As interventional radiologists in our trial were allowed to use anti-thrombotic agents for this indication, we cannot answer questions regarding the safety and efficacy of this treatment strategy. Also, we cannot make definite statements on the routine use of lower dosages of anti-thrombotic agents or a single bolus of heparin. We evaluated generally used dosages, but in clinical practice lower dosages are also used.[3] However, with the results of this trial, it seems advisable to further evaluate the use of lower dosages before it remains or becomes common practice.

Our trial had limitations. First, the early termination limits the precision of the effect estimates on the primary outcome. However, an effect more than twice as large as assumed in the sample size estimation had to occur in the second half of the trial to compensate for the adverse effects in the first half. The data safety and monitoring board and trial steering committee considered this very unlikely. Second, clinicians were aware of treatment allocation, which might have influenced post-intervention patient management. However, we took care to have all serious adverse events, all baseline and follow-up imaging, as well as all outcome assessments at 3 months assessed by independent committees, who were masked to treatment allocation. This approach minimised a potential bias in the safety or efficacy outcomes. Third, we did not record nor correct for heparin use in pressure bags. However, we did advise interventionists to limit this use of heparin to a maximum of 2500 IU/L. We estimate that this corresponds to a maximum infusion of approximately 500 IU in total. Fourth, all trial sites participated in the MR CLEAN-NO IV trial, which ran largely parallel to our study.[26] Patients presenting early and directly to a participating intervention centre without contraindications for intravenous thrombolytics were included in MR CLEAN-NO IV and not in our

trial. This effect resulted in a relatively large percentage of patients in our trial who were transferred from a primary hospital. However, the median onset to groin puncture time was still relatively short (<3 h), and baseline characteristics suggest that the trial population is representative of clinical practice. Finally, we used deferred consent in order not to delay endovascular treatment and study treatment. Selective withdrawal of patients with a poor outcome might have introduced selection bias. However, a sensitivity analysis of the strictly anonymised safety registry showed comparable effect estimates.

In conclusion, periprocedural intravenous aspirin and unfractionated heparin in patients with ischaemic stroke treated with endovascular treatment are both associated with increased risk of symptomatic intracranial haemorrhage without evidence for a beneficial effect on functional outcome.

For the **data request form from the CONTRAST consortium** see https://www.contrast-consortium.nl/data-request-form/

For the **study protocol and statistical analysis** see https://www.mrclean-med.nl/

Contributors

RAvdG, VC, AvdL, DWJD, and BR designed the trial. WvdS did the statistical analysis with input from RAvdG, HFL, DN, AvdL, DWJD, and BR. WvdS wrote the first draft of the report with input from RAvdG, AvdL, DWJD, and BR. All authors contributed to the collection of data and to the writing of the manuscript, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. WvdS and RAvdG have accessed and verified the data.

Declaration of interests

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Data sharing

With publication, de-identified data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others upon reasonable request. Data can be requested with a proposal at the website of the CONTRAST consortium, or by sending an e-mail to the corresponding author. Study protocol and statistical analysis plan are available on the trial's website.

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