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Periprocedural Intravenous Heparin During Endovascular Treatment for Ischemic Stroke

Results From the MR CLEAN Registry

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***Background and Purpose*—**Intravenous administration of heparin during endovascular treatment for ischemic stroke may improve outcomes. However, risks and benefits of this adjunctive therapy remain uncertain. We aimed to evaluate periprocedural intravenous heparin use in Dutch stroke intervention centers and to assess its efficacy and safety.

***Methods*—**Patients registered between March 2014 and June 2016 in the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke), including all patients treated with endovascular treatment in the Netherlands, were analyzed. The primary outcome was functional outcome (modified Rankin Scale) at 90 days. Secondary outcomes were successful recanalization (extended Thrombolysis in Cerebral Infarction ≥2B), symptomatic intracranial hemorrhage, and mortality at 90 days. We used multilevel regression analysis to evaluate the association of periprocedural intravenous heparin on outcomes, adjusted for center effects and prognostic factors. To account for possible unobserved confounding by indication, we analyzed the effect of center preference to administer intravenous heparin, defined as percentage of patients treated with intravenous heparin in a center, on functional outcome.

***Results*—**One thousand four hundred eighty-eight patients from 16 centers were analyzed, of whom 398 (27%) received intravenous heparin (median dose 5000 international units). There was substantial between-center variability in the proportion of patients treated with intravenous heparin (range, 0%–94%). There was no significant difference in functional outcome between patients treated with intravenous heparin and those without (adjusted common odds ratio, 1.17; 95% CI, 0.87–1.56), successful recanalization (adjusted odds ratio, 1.24; 95% CI, 0.89–1.71), symptomatic intracranial hemorrhage (adjusted odds ratio, 1.13; 95% CI, 0.65–1.99), or mortality (adjusted odds ratio, 0.95; 95% CI, 0.66–1.38). Analysis at center level showed that functional outcomes were better in centers with higher percentages of heparin administration (adjusted common odds ratio, 1.07 per 10% more heparin, 95% CI, 1.01–1.13).

***Conclusions*—**Substantial between-center variability exists in periprocedural intravenous heparin use during endovascular treatment, but the treatment is safe. Centers using heparin more often had better outcomes. A randomized trial is needed to further study these effects. **(*Stroke*. 2019;50:2147-2155. DOI: 10.1161/STROKEAHA.119.025329.)**

Key Words: cerebral infarction ■ heparin ■ reperfusion ■ stroke ■ thrombectomy

About one-third of the patients with ischemic stroke caused by an intracranial large vessel occlusion do not recover to functional independence, despite early and complete recanalization by endovascular treatment (EVT).[1] Although EVT is successful in reopening large intracranial arteries, it does not always restore microvascular perfusion. This incomplete microvascular reperfusion, also described as the no-reflow phenomenon, has first been reported in animal studies.[2–4] One of the causes of microvascular obstruction is the formation of neutrophil extracellular traps, which are known to be

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*A list of all MR CLEAN Registry Investigators is given in the Appendix

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present in all thrombi of ischemic stroke patients irrespective of stroke cause.[5] neutrophil extracellular traps are resistant to r-tPA (recombinant tissue-type plasminogen activator), but experimental studies show that unfractionated heparin is able to dissolve neutrophil extracellular traps at the microvascular level.[6–9] The effect of unfractionated heparin on neutrophil extracellular traps in humans has not been evaluated. In the pre-EVT era, no benefit of heparin use on outcome in ischemic stroke patients was seen, with a concomitant 1.2% increase in occurrence of symptomatic intracranial hemorrhage (sICH).[10] However, as the rate of successful recanalization is high in patients treated with EVT, heparin is now more capable of penetrating the downstream microvessels and targeting the no-reflow areas. That heparin may contribute to the treatment effect of EVT is not a new concept but originates from cardiology practices: periprocedural heparin has been used since the first percutaneous coronary intervention performed in 1977 and is standard practice since then.[11] By contrast, heparin is not the standard anticoagulant in EVT for ischemic stroke, which might be related to the perceived risk of sICH. In a systematic literature review, we found that heparin use during EVT indeed seems to be associated with an increased risk of sICH, but this increase seems to be outweighed by a higher overall chance of a good functional outcome.[12] The risk-benefit ratio of periprocedural intravenous heparin in patients with ischemic stroke undergoing EVT is still unclear. The uncertainty regarding this risk-benefit ratio is also reflected in the wide variation in the use of heparin in randomized trials that investigated the effect of EVT.[13] We aimed to evaluate the use of intravenous heparin during EVT in Dutch stroke intervention centers and to assess its efficacy and safety.

Methods

Study Design

We used data from the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke), which is an ongoing, nationwide, multicenter, prospective, observational study, including all consecutive patients treated with EVT for ischemic stroke in the Netherlands. The complete methods and description of variables of the MR CLEAN Registry have been described elsewhere.[14] For the present study, we selected patients who were registered between March 2014 and June 2016 and adhered to the following criteria: age of ≥18 years; treatment in a center that participated in the MR CLEAN trial; presence of a proximal intracranial occlusion in the anterior circulation confirmed on noninvasive vascular imaging (intracranial carotid artery [internal carotid artery (terminus)], middle cerebral artery [M1/M2], anterior cerebral artery [A1/A2]); and groin puncture within 6.5 hours after symptom onset. The current observational study was guided by the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology).[15] Data cannot be made available, as no patient approval has been obtained for sharing coded data. However, syntax files and output of statistical analyses in R will be made available on request.

Unfractionated Heparin Administration

Heparin administration was defined as any intravenous dose of unfractionated heparin administered during EVT. We explored the variability in doses of heparin used and percentages of patients treated with heparin within and between centers and over time. When information on heparin administration was missing, we assumed no heparin was administered to the patient. We performed 2 sensitivity analyses on this matter. First, we compared baseline characteristics of the group of patients whom we assumed not to have been treated with heparin to the patients explicitly registered as not treated with heparin. Second, we performed a complete case analysis of the primary and secondary outcomes in patients explicitly registered as treated with heparin versus no heparin.

Outcome Measures

The primary outcome was functional outcome at 90 days (range 14 days either way), assessed with the modified Rankin Scale (mRS), which is a 7-point ordinal scale ranging from 0 no symptoms to 6 dead.[16] Secondary outcomes were good functional outcome (mRS ≤2) at 90 days, successful recanalization rate (extended Thrombolysis in Cerebral Infarction grade ≥ 2B) assessed by an independent imaging core laboratory, occurrence of sICH, defined as patient neurological deterioration (decline of 4 points or more on the National Institutes of Health Stroke Scale) and a compatible hemorrhage seen on imaging assessed by an independent imaging core laboratory (according to the Heidelberg criteria), mortality at 90 days, progression of ischemic stroke (resulting in a decline of at least 4 points on the National Institutes of Health Stroke Scale), new ischemic stroke (imaging of new brain infarction with corresponding clinical neurological deficit), extracranial hemorrhage, and cardiac ischemia (myocardial ischemia confirmed by ECG and release of appropriate biomarkers).

Statistical Methods

Differences in baseline characteristics were analyzed for both categorical and dichotomous variables using χ^2 statistics. Continuous data were assessed for normality both visually and by means of Kolmogorov-Smirnov testing. One-way ANOVA was used for parametric and Kruskal-Wallis for nonparametric testing. A P value of <0.05 was considered significant in all applied tests. All baseline data and outcomes that are reported are crude and not imputed. Any mRS score assessed within 30 days of symptom onset was considered invalid and treated as missing. For the purpose of unbiased estimation of associations of outcome with baseline characteristics, we replaced missing outcome values when missing in <10% of the patients (eg, mRS) by values derived from multiple imputation.[17] Multiple imputed data were used in the adjusted outcome analyses. We used multilevel logistic and ordinal regression analyses to compare outcomes of patients treated with and without periprocedural intravenous heparin, with center as random effect and relevant factors as fixed effects (ie, heparin use, age, sex, National Institutes of Health Stroke Scale at admission, prestroke mRS, antiplatelet use, direct oral anticoagulant use, coumarin use, previous stroke, diabetes mellitus, glucose level at baseline, international normalized ratio, baseline systolic blood pressure, occlusion segment, Alberta Stroke Program Early CT Score at baseline, collateral grading, treatment with intravenous alteplase, anesthesia type, preinterventional extended Thrombolysis in Cerebral Infarction (eTICI) score, intraarterial thrombolysis, and onset-to-reperfusion time). Effects are presented as (adjusted common) odds ratios (OR) with 95% CI. To account for possible confounding by indication, we also analyzed the effect of center preference to administer heparin, defined as percentage of patients treated with heparin in a center, on outcome. All statistical analyses were performed with R version 3.5.0 (R foundation for Statistical Computing, Vienna, Austria) with the packages: tableone, mice, Hmisc, ggplot, and ordinal.

Results

Patient Population

From the total cohort of 1627 patients, 1488 patients from 16 centers were included and analyzed, of whom 398 (27%) received intravenous heparin (Figure 1). Among patients who received intravenous heparin, the median dose was 5000 international units (IU), ranging from 1250 to 10000 IU (Figure I in the online-only Data Supplement). The percentage of patients within a center treated with intravenous

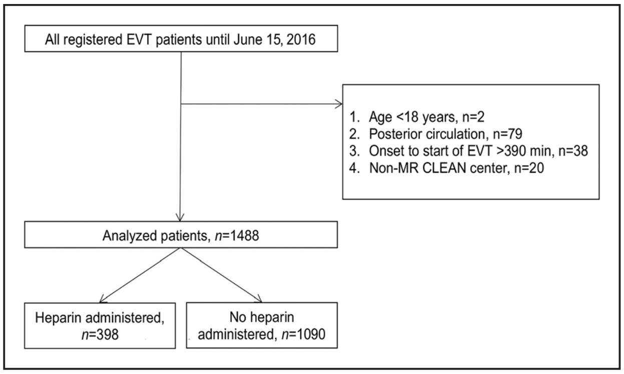

Figure 1. Flowchart. EVT indicates endovascular treatment; and MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke.

heparin ranged from 0% to 94% (Figure 2). Over the investigated time period, both the total proportion of patients receiving heparin and the proportion of patients receiving heparin per center remained stable (Figure II in the online-only Data Supplement). Patients receiving heparin presented more often with a stroke in the left hemisphere (233/398 [59%] versus 563/1090 [52%], *P*=0.03) and used coumarins less often (39/398 [10%] versus 151/1090 [14%], *P*=0.04; Table 1). Median time from emergency room admission at the intervention center to groin puncture (80 [51, 114] versus 66 [38, 99] minutes, *P*<0.01) and time from symptom onset to reperfusion (282 [225, 338] versus 265 [214, 327] minutes, *P*=0.01) were both longer in the heparin group. In the heparin group, patients received more often general anesthesia (215/398 [57%] versus 164/1090 [16%], *P*<0.01) and intra-arterial thrombolytics (33/398 [8.3%] versus 20/1090 [1.8%], *P*<0.01) during EVT. The sensitivity analysis showed no substantial baseline differences between patients in whom no heparin use was explicitly registered and those with missing heparin administration in whom we assumed no heparin was administered (Table I in the online-only Data Supplement).

Outcome Measures

No statistically significant difference in median mRS was observed between patients who received heparin and those who did not (3 [2, 6] versus 3 [2, 6]; adjusted common OR 1.17; 95% CI, 0.87–1.56; Figure 3). No statistically significant associations were found between heparin use and good functional outcome (adjusted odds ratio [aOR], 1.29; 95% CI, 0.88–1.88; Table 2), successful recanalization (aOR, 1.24; 95% CI, 0.89–1.79), sICH (aOR, 1.13; 95% CI, 0.65–1.99), and mortality (aOR, 0.95; 95% CI, 0.66–1.38). There were also no statistically significant differences between both groups in any of the other secondary outcomes. Multiple imputation was performed for 125/1488 (<10%) of the main outcome. The complete case analysis showed similar results (Table II in the online-only Data Supplement). The analyses of center preference to administer heparin showed that functional outcomes were better in centers with higher percentages of heparin administration (adjusted common OR, 1.07 per 10% increase in heparin use; 95% CI, 1.01–1.13 and for good functional outcome aOR 1.10 per 10% increase in heparin; 95% CI, 1.02–1.18; Table 3). In the center preference analyses, there was no association between an increase in heparin use and successful recanalization (aOR, 1.07; 95% CI, 0.96–1.19), sICH (aOR, 0.98; 95 % CI, 0.88–1.10), mortality (aOR, 0.95; 95% CI, 0.90–1.01), and other secondary outcomes.

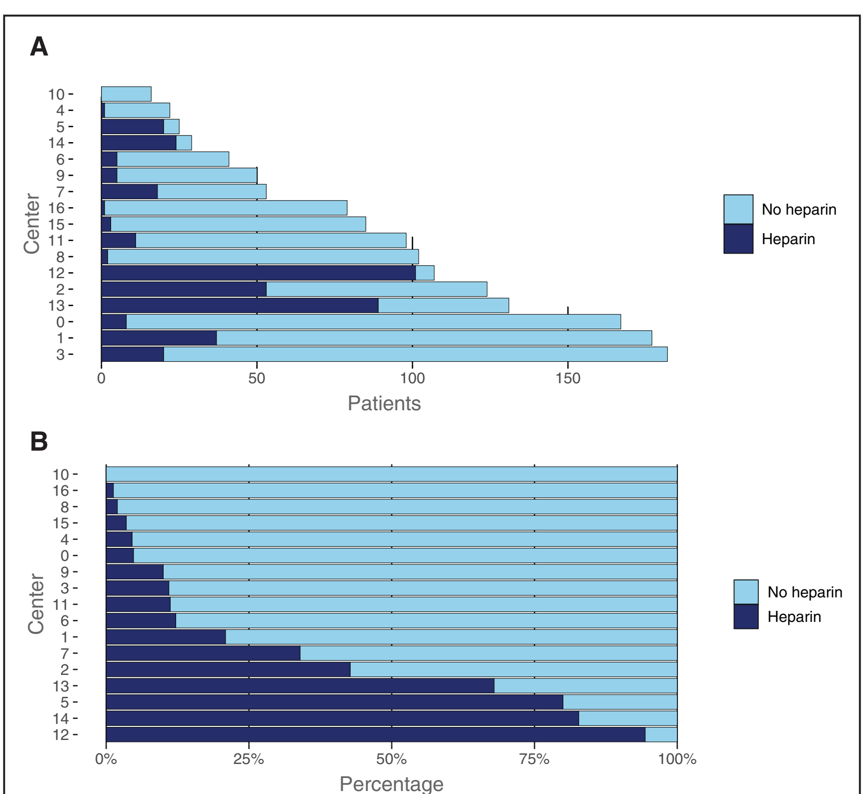

Figure 2. Heparin use during the total time period among Dutch stroke intervention centers in frequencies (**A**), and in percentages (**B**).

Table 1. Baseline Demographics

	Heparin (n=398)	No Heparin (n=1090)	*P* Value	Missing
Common patient characteristics				
Age, y	68 (15)	69 (14)	0.68	0
Male sex	206 (52%)	588 (54%)	0.49	0
NIHSS at baseline	16 [12–20]	16 [11–20]	0.77	18/12
Ischemia in left hemisphere	233 (59%)	563 (52%)	0.03	2/10
Systolic blood pressure	149 (25)	150 (24)	0.81	20/22
Diastolic blood pressure	81 (15)	82 (16)	0.56	19/28
Treatment with IV alteplase	300 (76%)	861 (79%)	0.16	1/2
INR	1.1 (0.4)	1.2 (0.4)	0.15	45/229
Glucose level	7.4 (2.3)	7.5 (2.7)	0.52	27/145
Trombocyte count	253 (90)	251 (93)	0.72	31/156
Center volume (patients treated per center per year)	55 [48–58]	55 [38–79]	0.08	0
Medical history				
Previous stroke	66 (17%)	183 (17%)	0.98	2/7
Atrial fibrillation	78 (20%)	249 (23%)	0.19	5/17
Hypertension	185 (47%)	560 (52%)	0.10	5/14
Diabetes mellitus	57 (14%)	198 (18%)	0.10	4/5
Myocardial infarction	58 (15%)	169 (16%)	0.74	9/20
Peripheral arterial disease	39 (10%)	96 (9.0%)	0.65	6/22
Prestroke mRS >2	57 (15%)	114 (11%)	0.05	8/19
Medication use				
Antiplatelet	140 (35%)	353 (33%)	0.44	1/18
DOAC	5 (1.3%)	32 (3.0%)	0.09	2/24
Coumarin	39 (10%)	151 (14%)	0.04	0/11
Blood pressure lowering medication	193 (49%)	568 (53%)	0.16	4/24
Statin	143 (36%)	379 (36%)	0.90	3/28
Imaging				
Occluded segment			0.11	20/55
Intracranial ICA	28 (7%)	54 (5%)		
ICA-T	68 (18%)	245 (24%)		
M1	226 (60%)	599 (58%)		
M2	52 (14%)	123 (12%)		
Other (eg, M3, ACA)	4 (1.1%)	14 (1.4%)		
Reperfusion before intervention (eTICI)			0.34	27/111
0	308 (83%)	799 (82%)		
1	29 (7.8%)	56 (5.7%)		
2A	7 (1.9%)	31 (3.2%)		
2B	10 (2.7%)	28 (2.9%)		
2C	3 (0.8%)	16 (1.6%)		
3	14 (3.8%)	49 (5.0%)		
ASPECTS	9 [7–10]	9 [7–10]	0.81	14/51
ASPECTS ≤ 7	110 (29%)	324 (31%)	0.39	14/51

(*Continued*)

Table 1. Continued

	Heparin (n=398)	No Heparin (n=1090)	*P* Value	Missing
Collaterals			0.30	25/82
Grade 0–absent collaterals	27 (7.2%)	70 (6.9%)		
Grade 1–occluded area filling <50%	122 (33%)	339 (34%)		
Grade 2–occluded area filling >50% but <100%	157 (42%)	378 (38%)		
Grade 3–occluded area filling 100%	67 (18%)	221 (22%)		
Workflow (in minutes)				
Time from symptom onset to admission ER (intervention center)	133 [68–190]	135 [59–189]	0.73	20/53
Time from admission ER to groin puncture	80 [51–114]	66 [38–99]	<0.01	42/89
Duration procedure	62 [40–87]	65 [40–95]	0.07	34/123
Time from symptom onset to reperfusion	282 [225–338]	265 [214–327]	0.01	20/67
Procedural				
General anesthetic management	215 (57%)	164 (16%)	<0.01	18/85
Administration of intraarterial thrombolytic	33 (8.3%)	20 (1.8%)	<0.01	0

Baseline variables with heparin vs no heparin. Continuous data are presented as mean (SD) for normal distributed data or as median [IQR] for skewed data. Categorical data are presented as n (%). ACA indicates anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; DOAC, direct oral anticoagulant; ER, emergency room; eTICI, extended Thrombolysis in Cerebral Infarction including a 2C grade; ICA, internal carotid artery; ICA-T, ICA terminus; INR, international normalized ratio; IQR, interquartile range; IV, intravenous; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

Discussion

In the present observational study, substantial between-center variability was found in the percentage of patients treated with periprocedural intravenous heparin. We did not find a significant effect of intravenous heparin use on functional outcome at the level of the individual patient. After mitigating potential unmeasured confounding by indication through analysis at the center level, we found a modest beneficial effect of heparin on functional outcome. Patients in centers that treat more patients with intravenous heparin had better functional outcomes, without increased sICH risk.

One of the first studies that introduced periprocedural use of intravenous heparin during EVT (by means of intraarterial prourokinase) was the PROACT II trial (Prolyse in Acute Cerebral Thromboembolism II), in which a nonsignificant increase in the risk of sICH was observed in the EVT arm compared with the control arm, with an improvement in functional outcome (significant after stratification for stroke severity).[18] Patients in both arms received a total dose of 4000 IU of heparin. Afterward several EVT trials implemented this as part of their protocol with doses ranging from 2000 to 5000 IU, whereas other trials did not.[12,13] The uncertainty regarding the risk-benefit ratio and absence of recommendations in the guidelines explains the variability in periprocedural intravenous heparin use in Dutch stroke intervention centers.[19] In prior studies on periprocedural heparin use, the doses used are comparable to the median dose of 5000 IU of heparin in this study.[13,20–22] Furthermore, we found that patients receiving heparin were less often on coumarins, which suggests that interventionists are more cautious to administer heparin in anticoagulated patients because of an allegedly higher sICH risk or the indication to administer heparin has already been treated by the coumarin. By contrast, we found that patients who received heparin were more likely to receive intraarterial thrombolytics, which could probably be related to center policy. This might also be the case for general anesthesia, which was also more often used in the heparin group. The longer emergency room to groin puncture time in the heparin group may be explained by the fact that heparin was less often used in the 3 largest centers, in which the workflow may be

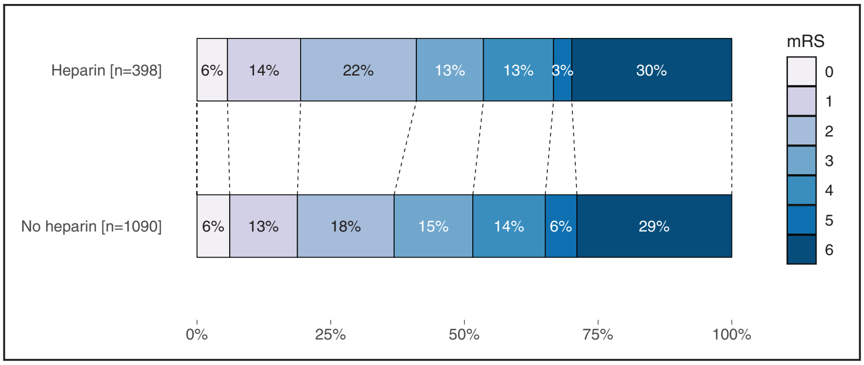

Figure 3. Primary outcome on the modified Rankin Scale (mRS) at patient level.

Table 2. Secondary Outcomes in Patients Treated With Heparin vs No Heparin

	Heparin (n=398)	No heparin (n=1090)	*P* Value	(c)OR, (95% CI)	a(c)OR (95% CI)*
mRS ≤ 2 at 90 days	144 (41%)	373 (37%)	0.19	1.19 (0.93–1.53)	1.29 (0.88–1.88)
Reperfusion after intervention (eTICI ≥2B)	245 (62%)	604 (56%)	0.05	1.28 (1.01–1.62)	1.24 (0.89–1.71)
Symptomatic intracranial hemorrhage	25 (6.3%)	61 (5.6%)	0.71	1.13 (0.70–1.83)	1.13 (0.65–1.99)
Mortality at 90 days	105 (30%)	293 (29%)	0.78	1.05 (0.80–1.37)	0.95 (0.66–1.38)
Progression of stroke	40 (10%)	100 (9.2%)	0.68	1.11 (0.75–1.63)	0.89 (0.54–1.45)
New ischemic stroke	7 (1.8%)	17 (1.6%)	0.97	1.13 (0.47–2.75)	0.80 (0.26–2.46)†
Extracranial hemorrhage	13 (3.3%)	20 (1.8%)	0.14	1.81 (0.89–3.67)	1.66 (0.68–4.05)
Cardiac ischemia	5 (1.3%)	7 (0.6%)	0.40	1.97 (0.62–6.24)	2.05 (0.49–8.48)‡

Primary and secondary outcomes in patients treated with heparin vs. no heparin. Categorical data are presented as numbers (%). a(c)OR indicates adjusted (common) odds ratio; ASPECTS, Alberta Stroke Program Early CT Score; (c)OR, (common) odds ratio; eTICI, extended Thrombolysis in Cerebral Infarction; INR, international normalized ratio; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Variables in the model: (fixed effects) heparin use, age, sex, NIHSS at admission, prestroke mRS, intravenous alteplase, preinterventional eTICI score, antiplatelet use, direct oral anticoagulant use, coumarin use, previous stroke, diabetes mellitus, intraarterial thrombolysis, glucose at baseline, systolic blood pressure, anesthesia type, occlusion segment, ASPECTS at baseline, INR, onset to reperfusion, collateral grading, time per month (random effect) center.

†Direct oral anticoagulant use not in model due to lack of convergence.

‡Intraarterial thrombolysis not in model due to lack of convergence.

more optimized in comparison to the workflow of the other centers. The median duration of the procedure was, however, comparable between groups.

Two smaller post hoc analyses of randomized controlled trials (Multi MERCI [Multi Mechanical Embolus Removal in Cerebral Ischemia] and TREVO-II [Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke II]) investigating the effects of EVT also addressed the question of whether periprocedural heparin is beneficial.[21,22] In both studies, periprocedural intravenous heparin use was associated with higher rates of good functional outcomes. The beneficial effect might be explained by the ability of intravenous heparin to restore incomplete microvascular reperfusion. The use of periprocedural heparin seems safe. In all our analyses, there was no statistically significant association between heparin use and sICH or mortality. This is also in line with the findings of the 2 aforementioned post hoc analyses of trials, which, however, did not adjust for risk factors for sICH. Finally, it is important to realize that periprocedural use of heparin is not novel in EVT practices as heparin has been used ever since the introduction of percutaneous coronary intervention in cardiology.[23] The rationale for heparin use during percutaneous coronary intervention is that the intervention is associated with factors that predispose to thrombosis (eg, stasis within the coronary artery, stasis within the catheters, and exposure of blood coagulation factors to injured endothelium, catheters, and guidewires) and is, therefore, used as part of protocol care.[11] One reason why neuro-interventionists have not fully adopted heparin use in current practice might be the fear of sICH, which, based on our results, seems to be unjustified.

Given the variability in heparin administration among Dutch stroke intervention centers and the promising results regarding outcome, a randomized controlled trial is warranted to prospectively evaluate adjunctive therapy and assess whether this is beneficial. In the ongoing trial MR CLEAN-MED (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; the Effect of Periprocedural Medication: Heparin, Antiplatelet Agents, Both or Neither, ISRCTN76741621), patients are randomized to intravenous heparin and/or acetylsalicylic acid to investigate whether this will affect microvascular reperfusion and improve functional outcome. Our observational study showed a nonsignificant absolute difference of 4% in good functional outcome (mRS 0–2)

Table 3. Primary and Secondary Outcomes Associated With Percentage Heparin Use Per Center (Per 10% Heparin Increase)

	a(c)OR, (95% CI; per 10% Heparin Increase)*
Primary outcome	
mRS at 90 days	1.07 (1.01–1.13)
Secondary outcomes	
mRS ≤ 2 at 90 days	1.10 (1.02–1.18)
Reperfusion after intervention (eTICI ≥ 2B)	1.07 (0.96–1.19)
Symptomatic intracranial hemorrhage	0.98 (0.88–1.10)
Mortality at 90 days	0.95 (0.90–1.01)†
Progression of stroke	1.00 (0.89–1.13)
New ischemic stroke	1.10 (0.84–1.44)‡
Extracranial hemorrhage	1.08 (0.90–1.29)
Cardiac ischemia	1.13 (0.82–1.55)†

Primary and secondary outcomes associated with 10% increase in percentage of patients treated with heparin at center level. a(c)OR indicates adjusted (common) odds ratio; ASPECTS, Alberta Stroke Program Early CT Score; eTICI, extended Thrombolysis in Cerebral Infarction; INR, international normalized ratio; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale.

*Variables in the model: (fixed effects) percentage heparin use per 10%, age, sex, NIHSS at admission, prestroke mRS, intravenous alteplase, preinterventional eTICI score, antiplatelet use, direct oral anticoagulant use, coumarin use, previous stroke, diabetes mellitus, intraarterial thrombolysis, glucose at baseline, systolic blood pressure, anesthesia type, occlusion segment, ASPECTS at baseline, INR, onset to reperfusion, collateral grading, time per month (random effect) center.

†Intraarterial thrombolysis not in model because of lack of convergence.

‡Direct oral anticoagulant use not in model because of lack of convergence.

in favor of heparin. This supports the sample size calculation of MR CLEAN-MED, which is powered to detect an absolute difference in good functional outcome of 5%.

Limitations

Because of the observational design of our study, confounding by indication could have influenced the results. For example, patient-related factors that are associated with the outcome could have influenced the treating physician's decision whether or not to administer heparin. For this reason, we adjusted for relevant prognostic factors that were likely to be associated with the administration of heparin. Furthermore, we performed an additional analysis in which we incorporated center preference to administer heparin to reduce the risk of possible unmeasured confounding by indication. In the latter analysis, confounding by indication at the interventionist level diminishes as the analysis at center level is less likely to suffer from this type of confounding (not decision or indication dependent). Also, this analysis takes into account specific center-related factors not included in the model—residual confounding—which could have influenced the physician's choice to administer heparin. However, even in this center preference analysis, some residual confounding might be present. Possible examples of residual confounding are that centers using heparin more frequently could have been better equipped or that interventionists administering heparin have more experience. Unfortunately, we could not adjust for this. Furthermore, as the distribution of heparin use among centers varied widely, we considered it interesting to explore if center preference is actually the preference of the specific center or rather the preference of the specific interventionist within the center. However, because some interventionists work at different sites and as part of an intervention team with changing staff, it was not feasible to perform this more in-depth exploration. Another limitation regarding this study is that activated clotting times were not measured, leaving the question unanswered if activated clotting times were adequately influenced by the treatment.

Conclusions

Substantial between-center variability exists in intravenous heparin use during EVT procedures in patients with ischemic stroke, but treatment is safe. Patients treated in centers that treat more patients with intravenous heparin have better functional outcomes. A randomized trial is warranted to further study the effects of this treatment.

*Appendix

Coinvestigators MR CLEAN Registry

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