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Endovascular Treatment for Acute Ischemic Stroke in Patients on Oral Anticoagulants

Results From the MR CLEAN Registry

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Background and Purpose—The use of oral anticoagulants (OAC) is considered a contra-indication for intravenous thrombolytics as acute treatment of ischemic stroke. However, little is known about the risks and benefits of endovascular treatment in patients on prior OAC. We aim to compare outcomes after endovascular treatment between patients with and without prior use of OAC.

Methods—Data of patients with acute ischemic stroke caused by an intracranial anterior circulation occlusion, included in the nationwide, prospective, MR CLEAN Registry between March 2014 and November 2017, were analyzed. Outcomes of interest included symptomatic intracranial hemorrhage and functional outcome at 90 days (modified Rankin Scale score). Outcomes between groups were compared with (ordinal) logistic regression analyses, adjusted for prognostic factors.

Results—Three thousand one hundred sixty-two patients were included in this study, of whom 502 (16%) used OAC. There was no significant difference in the occurrence of symptomatic intracranial hemorrhage between patients with and without prior OACs (5% versus 6%; adjusted odds ratio, 0.63 [95% CI, 0.38–1.06]). Patients on OACs had worse functional outcomes than patients without OACs (common odds ratio, 0.57 [95% CI, 0.47–0.66]). However, this observed difference in functional outcome disappeared after adjustment for prognostic factors (adjusted common odds ratio, 0.91 [95% CI, 0.74–1.13]).

Conclusions—Prior OAC use in patients treated with endovascular treatment for ischemic stroke is not associated with an increased risk of symptomatic intracranial hemorrhage or worse functional outcome compared with no prior OAC use. Therefore, prior OAC use should not be a contra-indication for endovascular treatment. **(*Stroke*. 2020;51:1781-1789. DOI: 10.1161/STROKEAHA.119.028675.)**

Key Words: anticoagulants ■ intracranial hemorrhage ■ outcome ■ stroke ■ thrombectomy

Oral anticoagulant agents (OAC) are used to reduce the risk of embolic complications. Paradoxically, whenever an embolic complication as ischemic stroke occurs, the perceived risk of hemorrhagic complications limits the options for acute reperfusion therapy. As such, intravenous thrombolytics (IVT) for acute ischemic stroke are contra-indicated for patients taking direct anticoagulants (DOACs) and vitamin K antagonists (VKAs) with international normalized ratio (INR) above 1.7.[1] For patients with ischemic stroke caused by an intracranial large vessel occlusion in the anterior circulation, endovascular treatment (EVT) is the only effective alternative.[2–5] However, it is not known whether prior use of OAC affects outcomes after EVT. In a single-center retrospective study, hemorrhage rates after EVT in patients ineligible for intravenous thrombolysis were similar for patients who were anticoagulated and patients not on anticoagulant therapy.[6]

The aim of the present study was to compare outcomes after EVT between patients with and without prior use of

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OACs in a large cohort representative of Dutch clinical practice.

Methods

Data Availability Statement

Source data will not be made available because of legislative issues on patient privacy. However, detailed analytic methods and study materials, including log files of statistical analyses, will be made available to other researchers on reasonable request to the corresponding author.

Study Design and Patient Population

Patients enrolled in the MR CLEAN Registry (Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands) from March 2014 until November 2017 were included in this study. The MR CLEAN Registry is a multicenter, prospective, observational cohort with EVT treated patients in the Netherlands.[5] All patients undergoing an EVT procedure (defined as entry into the angiography suite and arterial puncture) for acute ischemic stroke in the anterior and posterior circulation have been registered in the MR CLEAN Registry. EVT consisted of arterial catheterization with a microcatheter to the level of the occlusion, followed by mechanical thrombectomy with or without delivery of a thrombolytic agent. For the present study, we used the following inclusion criteria: arterial puncture within 6.5 hours after symptom onset; age ≥18; occlusion of intracranial carotid (ICA, ICA-T), middle (M1/M2) or anterior (A1/A2) cerebral artery, demonstrated by baseline CT angiography, treatment in a MR CLEAN trial center, and available data on prior OAC use. ASPECT score on baseline noncontrast CT and collateral status on CT angiography were scored using definitions described previously.[7,8] A central medical ethics committee evaluated the study protocol of the MR CLEAN Registry and granted permission to perform the study as a registry.

Prior OAC Use

Anticoagulant use before EVT was defined as any VKA or DOAC use before the EVT as reported on the case report form of the MR CLEAN Registry (www.mrclean-trial.org). INR was reported by local investigators, which was taken from blood samples at baseline before administration of IVT (if indicated). Anti-Xa activity, diluted thrombin time, and activated partial thromboplastin time were not measured routinely.

Outcome Measures

Outcomes of interest were reperfusion grade according to postintervention digital subtraction angiography, postintervention neurological deficit, occurrence of symptomatic intracranial hemorrhage (sICH), ischemic stroke progression, functional outcome, and mortality at 90 days. Reperfusion was scored by the extended Thrombolysis in Cerebral Ischemia (eTICI) score,[9] which ranges from grade 0 no reperfusion to grade 3 complete reperfusion. An independent core lab, blinded for clinical outcome, assessed all imaging.

Postintervention neurological deficit was measured with the National Institutes of Health Stroke Scale (NIHSS) score, with higher scores indicating greater deficit.[10]

An intracranial hemorrhage was considered symptomatic if the patient had died or had deteriorated neurologically (a decline of at least 4 points on the NIHSS), and the hemorrhage was related to the clinical deterioration (according to Heidelberg criteria[11]). Ischemic stroke progression was defined as neurological deterioration of at least 4 points on the NIHSS, in which an intracranial hemorrhage was excluded with CT as the cause of the deterioration. Functional outcome was measured with the modified Rankin Scale (mRS) score at 90 days, ranging from 0 no symptoms to 6 death.[12]

Missing Data

Missing NIHSS scores were retrospectively scored with a standardized score chart based on information from the reported neurological examination. If successful reperfusion was not achieved during EVT, the time of last contrast bolus injection was used as a proxy for time of reperfusion. Any mRS score of 0 to 5 assessed within 30 days was considered missing. These values were, therefore, replaced by mRS scores derived from multiple imputation for the (multivariable) regression analysis.[13] All descriptive analyses include patients with complete data, while all regression models include all patients with imputed data.

Statistical Analysis

Baseline characteristics were analyzed using standard statistics. We used ordinal logistic regression models to determine the association between OAC use and post-EVT reperfusion grade (eTICI) and functional outcome (mRS) at 90 days, and binary logistic regression models for the associations with sICH, ischemic stroke progression, and 90-day mortality. To estimate the association of OAC use with the NIHSS score 24 to 48 hours postintervention, we used linear regression models. Analyses were adjusted for important prognostic factors: age, baseline NIHSS score, prestroke mRS score, time from onset to start of EVT, intravenous thrombolysis, history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, and prior use of antiplatelet agents. In the case of clinical outcomes (ie, NIHSS score, functional outcome, sICH, stroke progression, and mortality), we additionally adjusted for systolic blood pressure, baseline collateral status, and ASPECT score. To compare functional outcome between patients with or without prior OAC use, we analyzed the shift on the mRS with ordinal logistic regression analysis.

Additionally, we performed subgroup analyses to evaluate the effect of the specific OAC types (ie, VKAs and DOACs) on the outcomes. Besides, we compared outcomes in patients with prior VKA use according to INR subgroups (INR ≤1.7; 1.7–3.0; >3.0). Statistical analyses were performed with Stata/SE 14.1 (StataCorp, TX).

Results

Patient Characteristics

Between March 2014 and November 2017, 3637 patients were enrolled in MR CLEAN Registry. After exclusion of patients with age <18 (n=9), treatment in a non-MR CLEAN trial center (n=177), posterior circulation occlusion (n=172), onset to start of EVT >390 minutes (n=99), and missing information on OAC use (n=18), we included 3162 patients for the current study (Figure 1). Before EVT, OACs were used in 502 patients (16%), of whom 404 patients were on VKAs and 98 on DOACs. Median INR among VKA users was 1.8 (interquartile range, 1.4–2.3).

Patients on OACs were older (median age 78 versus 71, $P<0.01$), had more severe neurological deficits at baseline (median NIHSS 17 versus 16, $P<0.01$), more comorbidities (ie, atrial fibrillation (78% versus 13%, $P<0.01$), diabetes mellitus (20% versus 15%, $P=0.02$), hypertension (64% versus 49%, $P<0.01$), hypercholesterolemia (34% versus 29%, $P<0.01$)), and were less often treated with antiplatelet agents before current stroke (11% versus 35%, $P<0.01$; Table 1). Patients on OACs more often had suffered from stroke in their medical history (28% versus 15%, $P<0.01$), and prestroke functional status was worse compared with patients not on OACs (pre-mRS 0 in 49% versus 70%, $P<0.01$). IVT were less frequently administered in patients on prior OACs (34% versus 84%; $P<0.01$). ASPECT score was slightly better in patients on OACs, with a score of 8 to

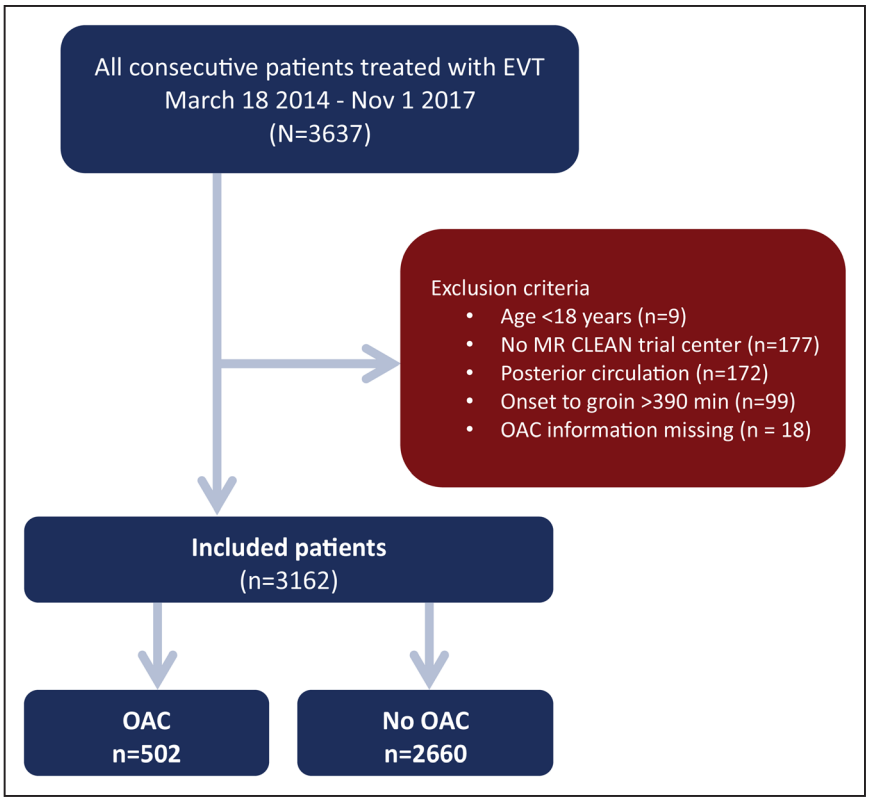

Figure 1. Flowchart of patients included in the study. EVT indicates endovascular treatment; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands; and OAC, oral anticoagulant.

10 in 76% versus 72% in patients not on OACs (*P*=0.03). Occlusion locations and collateral scores were not statistically different between the groups.

Outcomes

The proportion of patients with successful reperfusion (eTICI 2B or higher) was similar in both groups (61% for patients on OAC versus 64% in patients not on OAC; adjusted odds ratio, 0.91 [95% CI, 0.70–1.18]), as well as the proportion of excellent (eTICI 2C or higher) and complete (eTICI 3) reperfusion (Table 2). Intervention characteristics are shown in Table I in the Data Supplement.

NIHSS score at 24 to 48 hours postintervention was higher in patients on OAC compared with patients not on OAC (median 12 versus 10; β, 0.91 [95% CI, 0.02–1.80]). This difference was not statistically significant after adjustment for prognostic factors (adjusted β, −0.46 [95% CI, −1.38 to 0.47]). The proportion of patients with improvement of 4 or more points on the NIHSS was not different between groups (45% versus 49%; adjusted odds ratio, 1.01 [95% CI, 0.78–1.31]).

There was no statistically significant difference in the occurrence of sICH between patients with and without prior OACs (5% versus 6%; adjusted odds ratio, 0.79 [95% CI, 0.46–1.35]). Death within 90 days occurred more often in patients on OAC (38% versus 25%; OR, 1.82 [95% CI, 1.49–2.23]) in the univariable analysis. However, after adjustment for prognostic factors, prior OAC use was not associated with an increased mortality at 90 days (adjusted odds ratio, 1.20 [95% CI, 0.91–1.60; Table 2).

The mRS scores at 90 days were available in 2953/3162 patients (93%). Functional independence (mRS score 0–2) was reached less often by patients using OAC (29% versus 43%; OR, 0.54 [95% CI, 0.43–0.67]; Table 2). Use of OACs was associated with a shift towards worse outcomes on the mRS in the unadjusted analysis (cOR, 0.57 [95% CI, 0.47–0.66]; mRS distribution is shown in Figure 2). However, there was no statistically significant difference after adjustment for baseline prognostic factors (acOR, 0.88 [95% CI, 0.71–1.10]; Table 2).

Subgroup and Sensitivity Analyses

The incidence of sICH was lower in patients on DOACs when compared with patients on VKAs (1/98, 1% versus 23/404, 6%). However, functional outcome did not differ between patients on DOACs and VKAs (Table II in the Data Supplement). In patients with prior VKA use, complication risk and functional outcome was similar for INR subgroups ≤1.7 and 1.7 to 3.0 (Table III in the Data Supplement). Only 8 patients presented with a baseline INR >3.0, of whom one patient reached functional independence. Five of these 8 patients died within 90 days, of whom one from sICH.

Discussion

In this observational study representative of Dutch clinical practice, one out of 6 patients who underwent EVT for ischemic stroke was on prior OACs. Although the postprocedural reperfusion status and risk of sICH were similar between patients on prior OAC use compared with patients without prior OAC use, outcomes were worse for OAC users with regard to neurological recovery and functional outcome at follow-up. However, these observed differences disappeared after adjustments for imbalances in baseline

Table 1. Baseline Characteristics of 3162 Patients Who Underwent EVT for Ischemic Stroke, Stratified for Prior OAC Use Versus No Prior OAC Use

	OAC n=502	Non-OAC n=2660	*P* Value	Missing, n (%)
Age, median (IQR)	78 (69–84)	71 (60–80)	<0.01	0 (0)
Male sex, n (%)	262 (52)	1384 (52)	0.95	0 (0)
NIHSS, median (IQR)	17 (12–20)	16 (11–19)	<0.01	49 (2)
Clinical localization: left hemisphere, n (%)	285 (57)	1389 (52)	0.12	2 (0)
Systolic blood pressure, mean mm Hg (SD)	148 (26)	150 (25)	0.12	85 (3)
Intravenous alteplase treatment, n (%)	173 (34)	2239 (84)	<0.01	10 (0)
Medical history				
Atrial fibrillation, n (%)	394 (78)	359 (13)	<0.01	36 (1)
Hypertension, n (%)	322 (64)	1300 (49)	<0.01	60 (2)
Diabetes mellitus, n (%)	98 (20)	407 (15)	0.02	18 (1)
Hypercholesterolemia, n (%)	173 (34)	764 (29)	<0.01	131 (4)
Ischemic stroke, n (%)	143 (28)	387 (15)	<0.01	22 (1)
Prior antiplatelet use, n (%)	54 (11)	926 (35)	<0.01	27 (1)
Prestroke mRS score, n (%)			<0.01	71 (2)
0	248 (49)	1850 (70)		
1	96 (19)	309 (12)		
2	50 (10)	176 (7)		
>2	98 (20)	264 (10)		
Imaging				
Level of occlusion on noninvasive vessel imaging (CTA), n (%)			0.07	155 (5)
ICA (intracranial)	12 (2)	143 (5)		
ICA-T	109 (22)	525 (20)		
M1	280 (56)	1476 (55)		
M2	72 (14)	366 (14)		
Other: M3 and ACA	3 (1)	21 (1)		
ASPECTS subgroups			0.03	105 (3)
0–4, n (%)	14 (3)	129 (5)		
5–7, n (%)	87 (17)	540 (20)		
8–10, n (%)	381 (76)	1906 (72)		
Collaterals			0.31	202 (6)
Grade 0, n (%)	37 (7)	147 (6)		
Grade 1, n (%)	167 (33)	899 (34)		
Grade 2, n (%)	186 (37)	960 (36)		
Grade 3, n (%)	81 (16)	483 (18)		
Transfer from primary stroke center, n (%)	269 (54)	1467 (55)	0.51	1 (0)
Onset to arterial puncture (minutes), median (IQR)	190 (148–250)	195 (150–250)	0.56	14 (0)

ACA indicates anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; CTA, computed tomography angiography; EVT, endovascular treatment; ICA, internal carotid artery; ICA-T, internal carotid artery terminus; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and OAC, oral anticoagulant.

prognostic factors. Therefore, EVT should not be withheld in prior OAC users.

Several observational studies reported on the prevalence of OAC use in patients eligible for mechanical thrombectomy, which ranged from 3% to 23%.[14–24] The lowest prevalence was observed in studies which included patients from a very early period, from 1992 to 2002, respectively.[15,17] Back then, EVT was new, which might have led to cautious attitude towards this treatment, resulting in exclusion of patients on OACs. Prevalence in our study was in the upper range, with 16% of

Table 2. Outcomes of 3162 Patients Who Underwent EVT for Ischemic Stroke, Stratified for Prior OAC Use Versus No Prior OAC Use

	OAC Use	Non-OAC Use	Effect Estimates (95% CI)*	
	(n=502)	(n=2660)	Unadjusted	Adjusted
sICH, n (%)	24 (5)	162 (6)	0.77 (0.50 to 1.20)	0.79 (0.46 to 1.35)
Hemorrhage type, n (%)				
PH2	5 (21)	94 (58)		
PH1	10 (42)	33 (20)		
rPH	1 (4)	22 (14)		
SAH	17 (71)	80 (49)		
IVH	5 (21)	74 (46)		
Ischemic stroke progression, n (%)	37 (7)	244 (9)	0.79 (0.55 to 1.13)	0.74 (0.48 to 1.15)
Mortality at 90 d, n (%)	190 (38)	662 (25)	1.82 (1.49 to 2.23)	1.20 (0.91 to 1.60)
mRS at 90 d, median (IQR)†	4 (2-6)	3 (2-6)	0.57 (0.47 to 0.66)	0.88 (0.71 to 1.10)
mRS 0–1 at 90 d, n (%)†	73 (15)	589 (24)	0.56 (0.43 to 0.73)	0.85 (0.60 to 1.19)
mRS 0–2 at 90 d, n (%)†	140 (29)	1058 (43)	0.54 (0.43 to 0.67)	0.86 (0.63 to 1.17)
mRS 0–3 at 90 d, n (%)†	206 (43)	1386 (56)	0.58 (0.47 to 0.70)	0.93 (0.70 to 1.23)
NIHSS postintervention (24 h), median (IQR)‡	12 (5 to 18)	10 (4 to 17)	β 0.91 (0.02 to 1.80)	β –0.46 (–1.38 to 0.47)
Improvement on the NIHSS of ≥4 points, n (%)	224 (45)	1297 (49)	0.85 (0.69 to 1.04)	1.01 (0.78 to 1.31)
Successful reperfusion (eTICI 2B or higher)§, n (%)	263 (61)	1440 (64)	0.86 (0.70 to 1.07)	0.91 (0.70 to 1.18)
Excellent reperfusion (eTICI 2C or higher)§, n (%)	187 (43)	979 (43)	0.99 (0.80 to 1.21)	1.07 (0.84 to 1.36)
Complete reperfusion (eTICI 3)§, n (%)	134 (31)	709 (31)	0.97 (0.78 to 1.22)	1.08 (0.83 to 1.40)

ASPECTS indicates Alberta Stroke Program Early CT Score; EVT, endovascular treatment; eTICI, extended Thrombolysis in Cerebral Ischemia; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; and sICH, symptomatic intracranial hemorrhage.

*(Common) odds ratios, unless otherwise indicated. Analyses were adjusted for age, baseline NIHSS score, prestroke mRS score, time from onset to start of EVT, intravenous thrombolysis, history of hypertension, diabetes mellitus, hypercholesterolemia, ischemic stroke, and prior antiplatelet use. In the case of clinical outcomes, we additionally adjusted for systolic blood pressure, baseline collateral status and ASPECTS.

†n=2953 (mRS score at 90 d was missing for 209 patients).

‡n=2841 (postintervention NIHSS score was missing for 321 patients).

§n=2685 (patients who underwent an attempt for thrombectomy).

EVT eligible patients on OACs, and consistent with current practice described in most recently reported studies.[21,23]

In theory, prior OAC use may facilitate successful reperfusion, as the pharmacological mechanism is to reduce fibrin formation and, therefore, might reduce thrombus formation. On the contrary, achievement of successful reperfusion might be impaired by composition of the thrombus in cardio-embolic stroke (more prevalent in patients on OAC), which may be more difficult to retrieve.[25] Nevertheless, successful reperfusion was not significantly different between the groups in our study, consistent with previous studies.[15,16,19–22,25]

As in the majority of previous studies evaluating prior OAC use in EVT treated patients, risk of sICH was not increased, and even lower for patients on OACs in our study.[14–17,19–22] This finding could partly be due to the fact that IVT was withheld more often in patients who were on prior OACs (34% versus

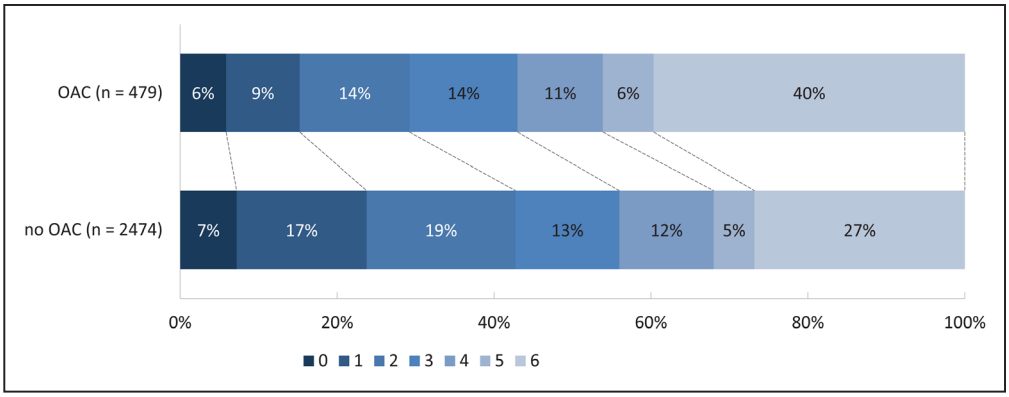

Figure 2. Functional outcome on the modified Rankin Scale (mRS); n=2953 (mRS score at 90 d was missing for 209 patients). OAC indicates oral anticoagulant.

84% in no OAC users), which may have resulted in a lower bleeding risk in this group. Nevertheless, after adjustment for IVT in regression analyses, the association with lower risk of sICH for patients on OAC persisted.

A previous meta-analysis showed that patients on OACs reached functional independence less often compared with nonusers.[26] In line with our study, this difference could not be explained by differences in recanalization or occurrence of sICH, but by older age and more cardiac co-morbidity. Three observational studies, thereafter, reported similar findings to our study with respect to functional outcome.[6,22–24] One multicenter study from the Madrid Stroke Network, however, reported similar functional outcome.[21] In this study, DOAC use was suggested to have a positive influence compared with the most frequently reported use of VKAs. However, only 8% of OAC users were on DOACs, compared with 20% in our study. Other explanations could have been baseline imbalances concerning right hemispheric and vertebrobasilar stroke, and lower NIHSS score in patients on OACs in that study.

Only few small observational studies investigated the relation between INR and risk of sICH after EVT. Increasing INR did not result in higher risk of ICH according to a small observational study.[20] Three small observational studies included 18, 21, and 10 patients who underwent EVT with INR >1.7.[17,27,28] In these studies, the risk of sICH or poor functional outcome were not increased for patients with INR >1.7. Only in one other small 2-center study with 21 patients, occurrence of sICH was increased (18% versus 7%) in patients with INR >1.7, but the difference was not significant. In our study, we found similar sICH rate and functional outcome compared with patients on VKAs with INR ≤1.7. Of note, only 8 patients with INR >3 were included in the study. Even though 5 of these patients died, only one died from sICH, which suggests hemorrhagic diathesis was not the primary cause of death. Nevertheless, strong conclusions about the safety of EVT in patients with INR >3 should not be drawn from this small sample size.

This study has some limitations. First, we reported observational, nonrandomized data. This might have resulted in confounding by indication, because patients on OACs were mainly patients with risk of cardio-embolic stroke and had cardiac co-morbidity with potential influence on outcomes. We adjusted for these prognostic factors in the regression analyses. However, this confounding may not be eliminated completely. Second, we were unable to report the time elapsed between administration of OACs and puncture for EVT. This may have had influence on hemorrhagic diathesis during and after the interventional procedure. Third, patients who were excluded from receiving EVT because of OAC use were not registered. However, we expect this number to be limited because in Dutch practice the standard is to treat patients with thrombectomy regardless of OAC use and an INR up to 3, or in some centers without INR limit.

Conclusions

Prior OAC use is not associated with an increased risk of sICH or worse functional outcome in patients treated with EVT for acute ischemic stroke compared with no prior OAC use. Therefore, prior OAC use should not be a contra-indication for EVT.

Appendix

MR CLEAN Registry Investigators—Group Authors

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