Continuation or Discontinuation of Anticoagulation in the Early Phase After Acute Ischemic Stroke

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Background and Purpose—There is no consensus on whether anticoagulation should be continued or temporarily stopped in patients suffering acute ischemic stroke while using anticoagulation. We assessed treatment variations and outcomes in these patients.

Methods—Post hoc analysis of PASS (Preventive Antibiotics in Stroke Study). We included patients with acute ischemic stroke who used anticoagulation at admission. We compared clinical outcomes, thrombotic, and major bleeding events at 3 months.

Results—Nine percent (192/2101) of the patients with acute ischemic stroke used anticoagulation at admission (186 vitamin K antagonists). Anticoagulation was discontinued in 35/192 (18%) patients. These patients had higher National Institutes of Health Stroke Scale scores than patients in whom anticoagulation was continued (median, 13 versus 4; $P<0.001$). Thrombotic events occurred more frequently in patients in whom anticoagulation was discontinued (11% versus 3%; $P=0.038$). There were no major bleeding events in either group. Mortality and clinical outcomes at 90 days were worse in patients in whom anticoagulation was discontinued (mortality, 31% versus 15%; $P=0.019$ and modified Rankin Scale score of 0–2, 20% versus 55%; $P<0.001$). After adjustment for potential confounders, there were no statistically significant differences between groups.

Conclusions—In our study, clinicians tended to continue anticoagulation in patients with acute ischemic stroke. Discontinuation was associated with an increased risk of thrombotic events and worse clinical outcome. Risk of major bleeding was not increased in patients in whom anticoagulation was continued.

Clinical Trial Registration—URL: https://www.controlled-trials.com. Unique identifier: ISRCTN66140176.

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Key Words: anticoagulants ■ embolism ■ heparin ■ secondary prevention ■ stroke

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Anticoagulation substantially reduces the risk of acute ischemic stroke (AIS) in patients with atrial fibrillation (AF) and other sources of cardioembolism.[1] The absolute risk of AIS in patients with AF who use anticoagulation is around 1% to 2% per year.[2,3] When a patient who uses anticoagulation does develop AIS, the clinician needs to decide whether to continue or temporarily discontinue anticoagulation. Continuation may increase the risk of intracerebral hemorrhage, but discontinuation may increase the risk of recurrent AIS or other thrombotic events. Various studies have focused on when to start anticoagulation in patients with newly diagnosed AF,[4] but no studies have compared treatment strategies about continuation or discontinuation of anticoagulation in patients who suffer AIS while using anticoagulation.

To address this important clinical question, we performed a post hoc analysis of PASS (Preventive Antibiotics in Stroke Study), a large randomized trial among stroke patients in the Netherlands.[5] Our aims were (1) to explore treatment variations among neurologists about continuation or discontinuation of anticoagulation in patients with AIS who use anticoagulation at admission and (2) to compare outcomes and the risk of major bleeding and thrombotic events between patients in whom anticoagulation was continued versus discontinued.

Methods

We included all patients with AIS who used anticoagulation at admission from PASS.[5] The definition of anticoagulation was the use of vitamin K antagonist (VKA), direct oral anticoagulant (DOAC), body weight-adjusted low-weight molecular heparin in therapeutic dosage, or unfractionated heparin and an activated partial thromboplastin time >45. Bridging with another type of anticoagulant was scored as a continuation. Discontinuation was defined as temporary or permanent stopping of anticoagulation, with the exception of short-term (<24 hours) cessation because of treatment with intravenous thrombolysis. A switch to platelet aggregation inhibitors or prophylactic low-weight molecular heparin was scored as discontinuation. Further details of the Methods are provided in the online-only Data Supplement. The

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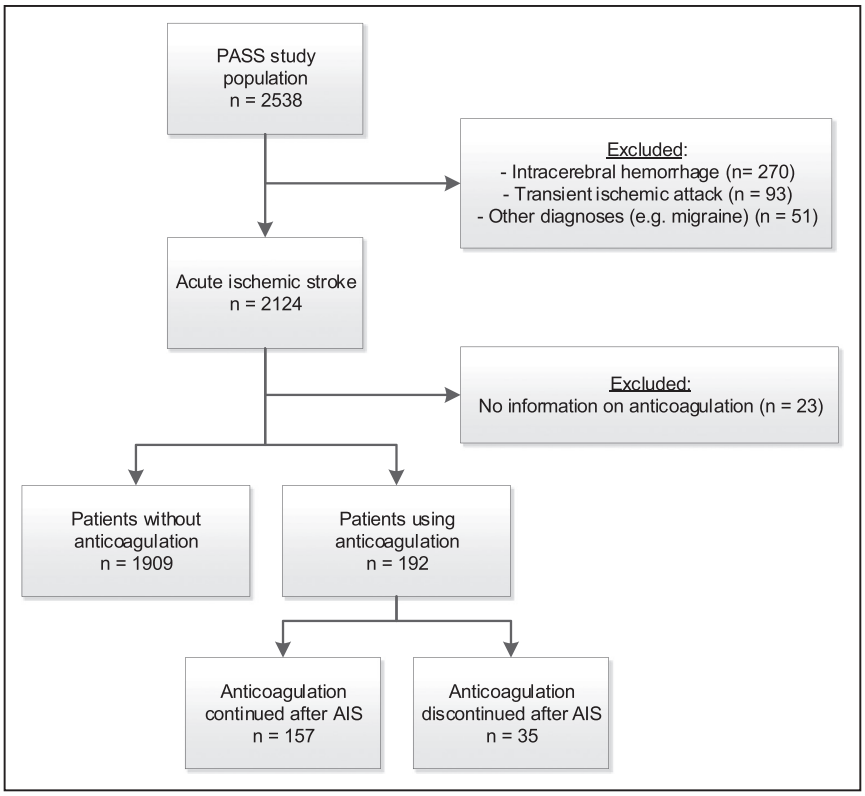

Figure. Flowchart for patient selection. AIS indicates acute ischemic stroke; and PASS, Preventive Antibiotics in Stroke Study.

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data that support the findings of this study are available from the corresponding author on reasonable request.

Primary end points were thrombotic or major bleeding events within 90 days after AIS. A thrombotic event was defined as an acute vascular occlusion of an extremity or organ, documented by imaging, surgery, or autopsy.[3] Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria. Secondary end points were mortality rate and functional outcome at 90 days, measured with the modified Rankin Scale.

We compared data of patients in whom anticoagulation was discontinued versus continued. We performed a sensitivity analysis in which we excluded patients who used VKA with an international normalized ratio <2. Intergroup comparisons were analyzed with Mann–Whitney test, χ^2 test, or Fisher exact test. We used multivariate logistic regression analysis, adjusting for variables that in univariate analysis differed between groups by P value <0.1. When there was no event recorded in one of the groups, univariate odds ratios were calculated by adding 0.5 to each of the cells in the 2×2 table.[6] If a patient suffered a thrombotic or bleeding event, the patient was censored for further events.

Results

Of 2124 patients with AIS included in PASS, 192 (9%) used anticoagulation at admission (Figure; Table I in the online-only Data Supplement). Types of anticoagulation were VKA (n=186, median international normalized ratio, 2.2), heparin (n=3), and DOAC (n=4). One patient used both VKA and heparin. Most common indications for anticoagulation were AF (159/192, 83%) and venous thromboembolism (11/192, 6%).

Anticoagulation was discontinued in 35/192 patients (18%). Discontinuation was temporary in 24/35 patients. Information on duration of cessation was available for 20 patients (median, 7 days; interquartile range, 4–9). One patient received prothrombin complex because of an international normalized ratio of 7.5. Patients in whom anticoagulation was discontinued had a higher National Institutes of Health Stroke Scale (NIHSS) score (median, 13 versus 4; P<0.001; Table 1). Among patients with a severe stroke (NIHSS>15), anticoagulation was stopped in 14/27 (52%) patients, compared with 21/165 (13%) of those with mild or moderate deficits (NIHSS≤15; P<0.001).

Patients in whom anticoagulation was discontinued more often suffered a thrombotic event within 90 days (11% versus 3%; P=0.038; Table 2). There were 2 recurrent AIS, both in the discontinuation group (P=0.032). One recurrent AIS occurred during carotid endarterectomy and one was because of cardioembolism. Major bleeding events did not occur in either group. Mortality and clinical outcomes at 90 days were worse in patients in whom anticoagulation was discontinued (mortality, 31% versus 15%; P=0.019 and modified Rankin Scale score of 0–2, 20% versus 55%; P<0.001). After adjustment for sex and NIHSS, there were no significant differences between groups. In the sensitivity analysis, discontinuation was associated with a lower chance of good outcome (adjusted odds ratio, 0.11; 95% confidence interval, 0.01–0.98; Table II in the online-only Data Supplement).

Discussion

In this post hoc analysis of a large stroke trial with broad inclusion criteria, 9% of patients with AIS used anticoagulation at admission. Anticoagulation was continued in ≈80% of patients, but in patients with severe neurological deficits (NIHSS>15), anticoagulation was temporarily stopped in only half. We found that discontinuation of anticoagulation was associated with a higher risk of recurrent AIS, mortality, and worse clinical outcome, but after adjustment for potential confounders, there were no statistically significant differences, suggesting residual confounding was an important explanation for the observed differences. Notably, continuation of

Table 1. Baseline Characteristics

	Discontinue (n=35)	Continue (n=157)	*P* Value
Male sex	15/35 (43)	102/157 (65)	0.015
Mean age±SD	79±9	78±10	0.829
Mean systolic blood pressure in mm Hg±SD	162±33	157±27	0.368
Mean diastolic blood pressure in mm Hg±SD	85±19	84±17	0.672
Median NIHSS (IQR)	13 (6–18)	4 (3–8)	<0.001
Intravenous thrombolysis	4/35 (11)	13/157 (8)	0.520
Medical history			
Atrial fibrillation	29/35 (83)	133/157 (85)	0.784
Prior stroke/TIA	13/35 (37)	76/157 (48)	0.227
Hypertension	18/34 (53)	105/155 (68)	0.101
Myocardial infarction	12/35 (34)	37/157 (24)	0.188
Diabetes mellitus	9/35 (26)	46/157 (29)	0.671
Type of anticoagulation*			
Vitamin K antagonist	33/35 (94)	153/157 (98)	0.301
Heparin†	1/35 (3)	2/157 (1)	0.455
DOAC	1/35 (3)	3/157 (2)	0.556
Stroke etiology (TOAST)			0.543
Large artery atherosclerosis	4/35 (11)	11/157 (7)	
Cardioembolism	26/35 (74)	103/157 (66)	
Small vessel disease	2/35 (6)	18/157 (12)	
Stroke of other determined cause	0/35	1/157 (1)	
Stroke of undetermined cause	3/35 (9)	24/157 (15)	
Prestroke mRS			0.439
0	13/35 (37)	83/157 (53)	
1	11/35 (31)	32/157 (20)	
2	6/35 (17)	23/157 (15)	
>2	5/35 (14)	19/157 (12)	

DOAC indicates direct oral anticoagulant; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; and TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

*There was one patient that used both vitamin K antagonist and heparin.

†Low-molecular weight or unfractionated heparin.

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anticoagulation was not associated with an increased risk of bleeding.

The American Heart Association guideline does not provide a recommendation whether to continue or discontinue anticoagulation.[1] The European Heart Rhythm Association guideline recommends the following algorithm about restart of anticoagulation: 1 day after transient ischemic attack, 3 days after mild stroke, 6 days after moderate stroke, and 12 days after severe stroke.[7] The majority of physicians in our study did not follow this recommendation. Anticoagulation was continued in 82% of all patients. In those with a severe stroke, there seems to be equipoise on the optimal strategy, because anticoagulation was discontinued in about half of the patients and continued in the other half.

Previous studies have focused on when to start anticoagulation in patients with acute stroke and newly diagnosed AF, although none focused on whether anticoagulation should be continued or discontinued in patients with acute stroke on anticoagulation therapy.[4,8] In these studies, the risk of thrombotic events was 6% in stroke patients in whom anticoagulation was started after ≈2 weeks and 11% in patients who did not received anticoagulation at all, which corresponds with the 11% observed in our study. The risk of bleeding was low in both studies, even in patients in whom anticoagulation was started after 4 to 5 days (0% to 5%).

Strengths of our study include the large sample size and completeness of the data set. Several limitations of our study warrant comment. First, the majority of patients used VKA as anticoagulation and the number of patients that used DOACs was small. The overall risk of intracerebral hemorrhage is lower with DOACs compared with VKA.[9] Future studies are required to determine whether DOACs can be safely continued

Table 2. Clinical Outcomes at 90 Days

	Discontinue (n=35)	Continue (n=157)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Thrombotic events	4/35 (11)	4/157 (3)	4.94 (1.17–20.80)	3.57 (0.67–19.07)
Recurrent ischemic stroke	2/35 (6)	0/157	23.51 (1.10–500.94)	NA
Other thrombotic events†	2/35 (6)	4/157 (3)	2.32 (0.41–13.19)	0.61 (0.07–5.26)
Major bleeding events	0/35	0/157	4.44 (0.09–227.40)	NA
mRS 0–2	7/35 (20)	85/156 (55)	0.21 (0.09–0.51)	0.50 (0.18–1.39)
Mortality	11/35 (31)	23/157 (15)	2.67 (1.15–6.18)	0.30 (0.08–1.14)

CI indicates confidence interval; mRS, modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.
*Adjusted for sex and NIHSS.
†Myocardial infarction (n=3), pulmonary embolism (n=2), and intestinal ischemia (n=1).

in patients with AIS. Second, although PASS had a large sample size, the number of patients using anticoagulation at baseline was low, as was the number of outcomes. In fact, none of the patients who used anticoagulation suffered major bleeding. Importantly, this suggests that the risk of major bleeding is low in this population, regardless of whether anticoagulation is continued or discontinued. Stroke severity is a strong predictor for hemorrhagic transformation and could be a possible explanation for the absence of bleeding in patients in whom anticoagulation was continued (indication bias).[10] Last, the results are not applicable to patients with AIS and a concurrent infection at baseline, because these patients were excluded from PASS.

Summary

In summary, this post hoc analysis of PASS shows that clinicians continue anticoagulation in most patients with AIS who use anticoagulation at admission. However, in those with severe neurological deficits, there seems to be equipoise. Discontinuation of anticoagulation was associated with a higher risk of thrombotic events, although this could not be verified in multivariate analysis. Continuation of anticoagulation was not associated with an increased risk of major bleeding.

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Disclosures

None.

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ONLINE SUPPLEMENT

Continuation or discontinuation of anticoagulation in the early phase after acute ischemic stroke

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Subject terms: Secondary Prevention, Anticoagulants, Cerebrovascular Disease/Stroke.

SUPPLEMENTAL METHODS

Preventive Antibiotics in Stroke Study

PASS was a nationwide, randomized controlled trial conducted in the Netherlands between 2010 and 2014. In total, 2538 patients with acute stroke were enrolled. The primary aim of PASS was to evaluate the efficacy of preventive antibiotics in stroke patients. Major inclusion criteria were: ischemic or hemorrhagic stroke, age ≥ 18 years old, National Institute of Health Stroke Scale (NIHSS) score ≥ 1, symptom onset < 24 hours, and admission to a neurological ward. Patients were randomized 1:1 between prophylactic ceftriaxone 2 gram daily for four days, or standard stroke care. The primary endpoint was functional outcome measured with the modified Rankin Scale (mRS) at 90 days, which was assessed by trained research nurses who were masked to treatment allocation of the patient. Detailed information on baseline characteristics, laboratory results, adverse events, and outcomes at 90 days was systematically recorded. The study protocol of the PASS was approved by the institutional review board of the Academic Medical Center and all patients or their next-of-kin provided written informed consent for participation in the study. The trial protocol of the PASS did not provide any recommendation on whether to continue or discontinue anticoagulation in patients with AIS.

Inclusion criteria current study

Definition of anticoagulation at the time of admission:

- Vitamin K antagonist
- Direct oral anticoagulant (DOAC)
- Body-weight adjusted low-weight molecular heparin (LMWH) in therapeutic dosage
- Unfractionated heparin and APTT > 45.

We excluded patients for whom there was no information available on anticoagulation use.

Definition of thrombotic or major bleeding event

A thrombotic event was defined as an acute vascular occlusion of an extremity or organ, documented by imaging, surgery or autopsy[1]. Major bleeding event was defined according to the International Society of Thrombosis and Haemostasis criteria[2].

SPSS version 23 was used for all analyses.

SUPPLEMENTAL TABLES

Online supplemental Table I. Comparison of baseline characteristics between patients with vs. without anticoagulation			
	Anticoagulation (n=192)	**No anticoagulation (n=1909)**	**P-value**
Male sex	117/192 (60.9)	1090/1909 (57.1)	0.305
Mean age ± SD	78 ± 9	71 ± 13	<0.001
Mean systolic blood pressure in mmHg ± SD	158 ± 29	164 ± 29	0.008
Mean diastolic blood pressure in mmHg ± SD	84 ± 17	86 ± 18	0.120
Median NIHSS (IQR)	5 (3 – 11)	5 (3 – 9)	0.169
Intravenous thrombolysis	18/192 (9.4)	784/1909 (41.1)	<0.001
Allocated ceftriaxone	92/191 (48.2)	941/1900 (49.5)	0.720
Medical history			
Atrial fibrillation	162/192 (84.4)	152/1905 (8.0)	<0.001
Prior stroke/TIA	89/192 (46.4)	607/1907 (31.8)	<0.001
Hypertension	123/189 (65.1)	1027/1908 (53.8)	0.003
Myocardial infarction	49/192 (25.5)	234/1907 (12.3)	<0.001
Diabetes mellitus	55/192 (28.6)	366/1908 (19.2)	0.002
SD, standard deviation; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale. Binary variables are presented as numbers with percentages.			

Online supplemental Table II. Sensitivity analysis including only patients with VKA and INR > 2				
	Discontinue (n=18)	**Continue (n=101)**	**Unadjusted OR (95% CI)**	**Adjusted OR* (95% CI)**
Thrombotic events	1/18 (6)	1/101 (1)	5.88 (0.35 – 98.60)	2.99 (0.11 – 85.18)
Recurrent ischemic stroke	1/18 (6)	0/101	17.40 (0.68 – 444.54)	NA
Other thrombotic event†	0/18	1/101 (1)	1.81 (0.07 – 46.18)	NA
Major bleeding events	0/18	0/101	5.49 (0.11 – 285.26)	NA
mRS 0-2	1/18 (6)	58/100 (58)	0.04 (0.01 – 0.33)	0.11 (0.01 – 0.98)
Mortality	6/18 (33)	14/101 (14)	3.11 (1.00 – 9.63)	0.34 (0.06 – 1.98)

ICH, intracranial hemorrhage; mRS, modified Rankin Score; OR, odds ratio; CI, confidence interval; NA, not applicable.
*Adjusted for baseline NIHSS score and history of myocardial infarction.
† Myocardial infarction.

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