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ORIGINAL ARTICLE

Monitoring of direct oral anticoagulants plasma levels for secondary stroke prevention

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Abstract

Background: Patients with atrial fibrillation have a relevant risk for ischemic stroke despite the recommended use of direct oral anticoagulants (DOAC). The risk correlates with the functional DOAC plasma levels in clinical trials, but the value of their measurement in community use remains undetermined.

Objectives: We aim to investigate the clinical implications and the prognostic value of DOAC plasma level measurement during steady state.

Methods: In this observational clinical cohort study among patients with ischemic stroke and atrial fibrillation, 397 individuals on oral anticoagulants for secondary stroke prevention were included between 2016 and 2020. The functional DOAC plasma levels were measured during steady state. Early stroke recurrence within 3 months was recorded as the main outcome parameter.

Results: Three hundred ninety-seven patients (201 female, mean age 78 [±9] years, median CHA_2DS_2VASc-Score 6 [interquartile range 5–7]) were included. Mean DOAC plasma trough level was 95.9 (±66.9) ng/ml. A high glomerular filtration rate (GFR) was an independent predictor of lower levels in a multivariate model (*R* coefficient: −0.174, $P = .014$). During follow-up, 10 patients (3%) suffered from early ischemic stroke recurrence despite the use of DOAC, while 10 clinically relevant bleeding complications occurred (3%). Ischemic stroke recurrence was associated with numerical lower plasma levels for patients on apixaban and dabigatran after propensity score matching.

Conclusions: Monitoring of DOAC plasma levels could help to identify patients with increased risk for stroke recurrence and should be considered for certain subgroups, including patients with high GFR.

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KEYWORDS
atrial fibrillation, cardioembolic stroke, direct oral anticoagulants, ischemic stroke, secondary prevention

1 | INTRODUCTION

Atrial fibrillation (AF) is a leading cause of ischemic stroke and strategies to improve primary and secondary prevention are warranted.[1,2] Direct oral anticoagulants (DOAC) are recommended over antiplatelet therapy and represent the standard of care for the majority of patients.[3,4] Despite the recommended use of DOAC for prevention of thromboembolism, patients remain exposed to a relevant risk of ischemic stroke.[5–8] Unlike Vitamin K antagonists, DOAC treatment does not demand any hemostaseologic routine monitoring. However, the plasma levels during steady state are characterized by a strong interindividual fluctuation, while the responsible factors for lower levels remain widely unexplored.[9] In addition, in prospective clinical trials the plasma trough and peak levels were monitored for all four substances available at present (apixaban, dabigatran, edoxaban, rivaroxaban)[9–12] and an association of low plasma levels and recurrent ischemic stroke was repeatedly reported.[9,10,13] The feasibility of plasma level measurements during steady state among stroke patients as well as the association of plasma levels with the risk of stroke recurrence have not been investigated sufficiently yet. The aim of this study was to identify the predictors of the functional DOAC plasma levels and to investigate their association with the risk of stroke recurrence in a real-world clinical cohort of patients with ischemic stroke and AF.

Essentials

- The clinical relevance of direct oral anticoagulant (DOAC) plasma levels for ischemic stroke recurrence in atrial fibrillation is undetermined.
- We investigated DOAC plasma levels in steady state in a clinical cohort study among 397 patients for secondary prevention of ischemic stroke.
- A high glomerular filtration rate is an independent predictor of lower DOAC plasma levels.
- Patients with recurrent ischemic stroke showed numerically lower trough levels for apixaban and dabigatran.

2 | PATIENTS AND METHODS

The anonymized data that support the findings of this study are available from the corresponding author on request. The protocol was approved by the ethics committee of the Faculty of Medicine, University of Erlangen-Nuremberg, Germany. The study conforms with the World Medical Association Declaration of Helsinki.

The data of this study were obtained from the Erlangen Registry of Patients on Oral Anticoagulation (ER-NOAC) as described previously.[14–16] We included consecutive patients with cerebral ischemia and AF, who were admitted to the Department of Neurology at the University Hospital Erlangen between August 2016 and March 2020. Additional inclusion criteria were the use of DOACs with measurements of their plasma levels during steady state available. The dataset included clinical and demographic characteristics at baseline, details on the acute care and secondary prevention, as well as the functional outcome after 3 months. Bleeding complications that required medical consultation were classified as "clinically relevant."

The treatment followed international recommendation guidelines and the dose regimens were chosen in accordance with the European Medicines Agency (EMA) label.[17–20] Functional plasma levels of DOAC were measured during steady state, defined as a minimum of 48 h of regular treatment with personally confirmed drug intake during the patient's in-hospital stay. The trough levels were collected 12+/−1 h (for apixaban and dabigatran) or 24+/−1 h later (for edoxaban and rivaroxaban).[21] Plasma levels were measured using anti-Xa-based chromogenic assays (STA-Liquid Anti-Xa, Diagnostica STAGO S.A.S.) with anticoagulant-specific calibration (Diagnostica STAGO S.A.S., France) or Hemoclot ® direct thrombin inhibitor assay (HYPHEN BioMed) for dabigatran, based on international recommendations.[21,22] The standard of care also included a renal function test on admission and the calculation of the glomerular filtration rate (GFR) using the Cockroft and Gault formula.

The statistical analysis was performed using the SPSS software (IBM SPSS Statistics 21). Normality of distribution was tested using the Kolmogorov-Smirnov test. To identify the clinical factors that are associated with the functional plasma level, a univariate analysis was calculated. The following factors were examined: age; baseline National Institutes of Health Stroke Scale (NIHSS); pre-stroke modified Rankin Scale score (mRS); body weight; CHA_2DS_2VASc-Score; GFR; sex; diabetes mellitus; alcohol consumption; liver disease; gastrointestinal passage disorder; and comedication with proton pump inhibitors, antiepileptics, or antibiotics. Factors with a trend toward significance ($P < .2$) were included in the multiple linear regression. The association between plasma trough levels with the risk of stroke recurrence was investigated after propensity score matching (1:5, nearest neighbor approach, with caliper 0.2). Patients with and without recurrent stroke were matched for established risk factors of recurrent ischemic stroke: age, NIHSS on admission of index stroke, pre-stroke mRS, heart failure, arterial hypertension, diabetes mellitus, hypercholesterinemia, body weight, and history of ischemic stroke.

3 | RESULTS

3.1 | Baseline characteristics

Three hundred ninety-seven patients (50.6% female) admitted with acute ischemic stroke or transient ischemic attack and AF were included. The mean age was 78 (±9) years, the median CHA_2DS_2VASc-Score was 6 (5–7 interquartile range [IQR]) and the NIHSS score on admission was 4 (1–8 IQR). The clinical and demographic characteristics at baseline are provided in Table 1. In 116 patients (29.2%) the anticoagulant prior to admission was continued with the substance and the established dose regimen remaining unchanged. In 281 patients (70.8%) an anticoagulant was started or switched from another substance, including 68 (17.2%) patients pretreated with a Vitamin K antagonist and 53 (38.5%) patients with no prior anticoagulation. Two hundred fifty-one patients (63%) used apixaban, 83 patients (21%) received dabigatran, 43 patients (11%) received edoxaban, and 20 patients (5%) received rivaroxaban. No major imbalances comparing the patients on the different substances regarding baseline characteristics were detected. Ninety-two (23.2%) received the lower/reduced dose according to the product labeling.[17–20] Plasma trough level was obtained after a median of 3 (3–5 IQR) days after first intake. The overall mean plasma trough level was 95.9 (±66.9) ng/ml.

3.2 | Predicting factors for low functional plasma levels

Twenty-four patients (6%) had a GFR <30 ml/min, 154 (38.8%) between 30 to 59 ml/min, 152 (38.3%) had a GFR between 60 to 94, and 67 (16.9%) had a GFR of 95 ml/min or higher. Figure 1 displays the inverse correlation between GFR and functional trough plasma level. Regarding different DOACs, all substances showed a trend toward an inverse correlation, though only dabigatran reached statistic significance (Apixaban: $r = -0.107$, $p = .097$; dabigatran: $r = -0.368$, $P = .001$; edoxaban: $r = -0.248$, $P = .109$; rivaroxaban: $r = -0.037$, $P = .881$; see Figure S1 in supporting information).

After univariate analysis, the following variables were included in a multivariate linear regression model: age, sex, pre-atroke mRS, CHA_2DS_2Vasc score, and GFR (see Table S1 in supporting information). Only the GFR proved to be an independent predictor of low plasma levels, meaning high GFR resulted in lower plasma trough levels (see Table 2).

3.3 | Low plasma trough levels are associated with recurrent stroke after 3 months

For 338 patients (85%) the 3-month follow-up was available; 59 (15%) were lost to follow-up. Baseline clinical characteristics of the patients that were lost to follow-up are given in Table S2 in supporting information. There are no major imbalances except a higher proportion of women.

Ten patients (3%) had a clinically relevant bleeding event. Six patients suffered from gastrointestinal bleeding, three patients from epistaxis, and one from oral bleeding. No intracranial bleeding and no fatal bleeding occurred. Plasma trough levels of patients with bleeding during follow-up did not differ (95.3 ± 67.1 ng/ml vs. 75.7 ± 67.6 ng/ml, $P = .388$).

Nineteen patients (4.8%) died during follow-up: causes of death were cardiovascular events other than ischemic stroke in nine patients (2.1%), one fatal recurrent ischemic stroke (0.3%), complications related to index stroke in eight patients (2.1%), and other/undetermined causes in two patients (0.6%). Plasma trough levels of patients who died during follow-up did not differ (94.8 [±67.1] vs. 88.8 [±49.6] ng/ml, $P = .720$).

Ten (3% of patients) had a recurrent ischemic stroke despite recommended DOAC use: one patient on edoxaban (2.4% of patients on the substance), three patients on dabigatran (3.6%), five patients on apixaban (2%), and one patient on rivaroxaban (5%). Outcome events for different DOAC groups with their respective plasma levels are given in Table 3. After propensity score matching, patients with recurrent stroke on apixaban and dabigatran had numerically lower plasma trough levels, while the differences did not reach statistical significance for the four single substances (see Figure 2, Table 4, and Figure S1).

4 | DISCUSSION

In this real-world clinical cohort, patients with ischemic stroke and AF received monitoring of the DOAC functional plasma levels for secondary prevention during in-hospital stay. There are two major findings: (1) The glomerular filtration rate on admission independently predicted lower plasma trough levels and (2) the rate of early stroke recurrence was associated with lower levels after adjustment for confounding factors.

The International Council for Standardization in Haematology has published results from DOAC plasma level measurements from different cohorts, mainly patients using the substances for primary stroke prevention.[21] When the results of our cohort are compared to those values, an overall good concordance can be ascertained. Notably, there is a broad range of fluctuation, resulting in a relevant number of patients with low or very low trough values prior to the next dose. It is therefore tempting to speculate, to what extent the absence of antithrombotic activity at the point of inflection could contribute to thrombogenesis and embolic complications.[13,23]

A number of clinical conditions was previously reported as predictors of low DOAC plasma levels, including high body weight and high GFR.[24] Consistently, our study confirmed the GFR as an independent predictor among patients using DOAC for secondary stroke prevention. For edoxaban, an inverse correlation between renal function and clinical efficacy has been established previously. The U.S. Food and Drug Administration (FDA) advises against the prescription of the substance among individuals with GFR >95ml/

TABLE 1 Clinical and demographic characteristics at baseline

General characteristics	Whole cohort	Patients on apixabam	Patients on dabigatran	Patients on edoxaban	Patients on rivaroxaban
N (%)	397	251 (63%)	83 (21%)	43 (11%)	20 (5%)
Female, *n* (%)	201 (50.6%)	129 (51.4)	38 (45.8%)	22 (51.2%)	12 (60%)
Age, mean (min–max) [years]	78.7 (32–100)	80.6 (48–100)	72 (32–94)	79 (56–93)	80.3 (54–91)
Body weight, mean (min–max), [kg]	78 (39–139)	77.4 (39–138)	80 (49–139)	78.9 (45–125)	74.5 (50–100)
GFR, mean (±SD), [ml/min]	68.6 (±29.9)	63.0 (±16.2)	82.3 (±34.1)	75.2 (±26.6)	68.0 (±28.4)
AF sustained/paroxysomal, *n* (%)	62 (15.6%) / 335 (84.4%)	48 (19.1%) / 203 (80.9%)	6 (7.2%) / 77 (92.8%)	3 (7%) / 40 (93%)	4 (20%) / 16 (80%)
CHA_2DS_2VASc, median (IQR)	6 (5–7)	6 (6–7)	5 (4–6)	6 (5–7)	6 (5–7)
Pre-stroke mRS, median (IQR)	0 (0–2)	1 (0–3)	0 (0–1)	0 (0–2)	1 (0–3)
Index event					
Ischemic stroke, *n* (%) / TIA *n* (%)	302 (76.1%) / 95 (23.9%)	192 (76.5%) / 59 (23.5%)	58 (69.9%) / 25 (30.1%)	38 (88.4%) / 5 (11.6%)	14 (70%) / 6 (30%)
NIHSS on admission, median (IQR)	4 (1–8)	4 (1–9)	2 (1–6)	4 (1–9)	3 (1–10)
i.v.-Thrombolysis, *n* (%)	74 (18.6%)	47 (18.7%)	16 (19.3%)	11 (25.6%)	0 (0%)
Mechanical thrombectomy, *n* (%)	50 (12.6%)	33 (13.1%)	11 (13.3%)	4 (9.3%)	2 (10%)
Comorbidities and Comedication					
History of ischemic stroke or TIA, (%)	142 (35.8%)	91 (36.3%)	25 (30.1%)	20 (46.5%)	6 (30%)
Arterial hypertension, *n* (%)	358 (90.2%)	227 (90.8%)	73 (88%)	39 (90.7%)	19 (95%)
Diabetes mellitus, *n* (%)	111 (28.0%)	80 (32%)	15 (18.1%)	11 (25.6%)	5 (25%)
Hypercholesterinemia, *n* (%)	337 (84.9%)	215 (85.7%)	67 (80.7%)	37 (86%)	18 (90%)
Active smoker, *n* (%)	36 (9.1%)	16 (6.4%)	14 (16.9%)	5 (11.9%)	1 (5%)
Active alcohol consumption, *n* (%)	55 (13.9%)	28 (11.2%)	18 (21.7%)	7 (16.3%)	1 (10%)
Liver disease, *n* (%)	6 (1.5%)	3 (1.2%)	2 (2.4%)	1 (2.3%)	0 (0%)
Gastrointestinal passage disorder, *n* (%)	15 (3.8%)	8 (3.2%)	4 (4.8%)	3 (7%)	0 (0%)
Protone Pump inhibitor treatment, *n* (%)	128 (32.25)	85 (33.9%)	21 (25.3%)	17 (39.5%)	5 (25%)
Antiepileptic treatment, *n* (%)	38 (9.6%)	24 (9.6%)	8 (9.6%)	3 (7%)	3 (15%)
Antibiotic treatment, *n* (%)	93 (23.4%)	71 (28.3%)	7 (8.4%)	12 (27.9%)	3 (15%)

Abbreviations: AF, atrial fibrillation; GFR, glomerular filtration rate as calculated by Cockcroft and Gault formula; IQR, interquartile range; mRS, modified Rankin Scale; *n*, number; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; TIA, transient ischemic attack.

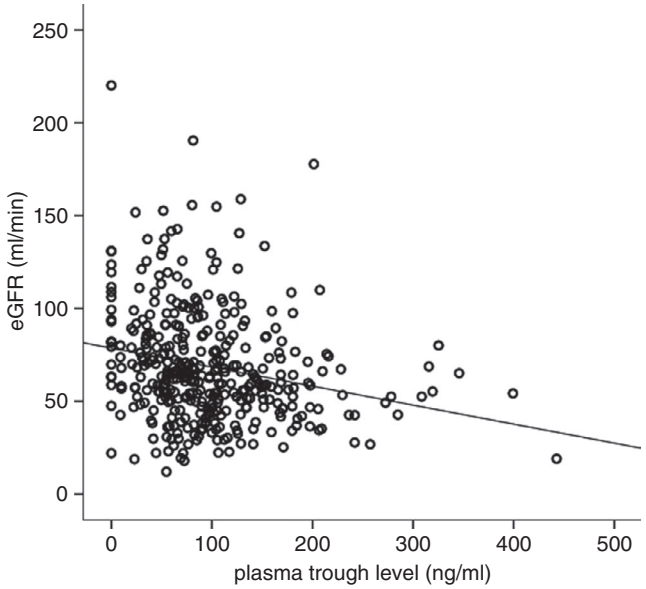

FIGURE 1 Association of renal function with plasma trough level. Low plasma trough levels were associated with high glomerular filtration rate (GFR) as calculated with Cockcroft and Gault formula

min, while the EMA label did not include an analogous restraint.[19,25] A recent German cohort study reported a superior benefit-risk profile of edoxaban compared to the other substances.[6] The authors suggested that this refers to the FDA restraint for individuals with GFR >95 ml/min, leading to a preferred use of the other substances among these patients likewise in Europe. Remarkably, a similar inverse relationship between renal function and efficacy might also apply to rivaroxaban and dabigatran, though a restraint was not included into the product label.[26–28]

Creatinine clearance above 95 ml/min occurred in approximately every sixth patient in our cohort, highlighting the particular relevance for clinical care. On the other hand, a number of factors were reported from previous studies that might potentially affect DOAC plasma levels.[29,30] However, none of those proved to be an independent predictor in our cohort, especially concomitant medication with antiepileptics or body weight did not reach significance.

Incidence rate of recurrent ischemic stroke was remarkably high in our study (3% in the first 3 months) compared to prospective trials with reported rates of 1.2%–1.3%/year.[11,12,31,32] However, our cohort used DOAC exclusively for secondary stroke prevention and therefore showed the expectedly higher rate of comorbidities

TABLE 2 Multivariate linear regression model of factors on plasma levels

	Regression coefficient	Standard error	Standardized coefficient *R*	*P*-value
Age	0.35	0.53	0.049	.510
Sex	−0.348	7.354	−0.003	.962
Pre-Stroke-mRS	0.3723	2.735	0.079	.174
CHA_2DS_2Vasc-Score	2.986	3.285	0.063	.364
GFR	−0.336	0.137	−0.174	**.014**

Note: *P*-values <.05 are considered significant. Bold value indicates differences statistical significant.

Abbreviations: GFR, glomerular filtration rate (Cockcroft and Gault formula); mRS, modified Rankin Scale.

TABLE 3 Outcome events for the four substances

	Bleeding in follow-up	Ischemic stroke in follow-up	Composite endpoint of stroke and death	No follow-up event
Apixaban, *n*	4	5	16	184
Plasma trough level, mean (min–max, ng/ml); *P*-value[a]	116.6 (49.7–210) *P* = .883	77.8 (45.9–121.5) *P* = .115	101 (45.9–209.1) *P* = .500	114.6 (0–399.3)
Dabigatran, *n*	5	3	4	58
Plasma trough level, mean (Min–Max, ng/ml); *P*-value[a]	66.4 (0–128.5) *P* = .821	29.1 (0–44.1) *P* = .128	29.5 (0–44.1) *P* = .073	79.2 (0–442.7)
Edoxaban, *n*	1	1	3	30
Plasma trough level, mean (min–max, ng/ml); *P*-value[a]	0	53.8	60.8 (49.8–78.9) *P* = .068	40.3 (0–135)
Rivaroxaban, *n*	0	1	3	15
Plasma trough level, mean (min–max, ng/ml); *P*-value[a]	-	58.8	38 (0–58.8) *p* = .824	47.9 (0–96.8)

[a]Using Mann-Whitney-test, for $n \geq 3$.

and risk factors (including higher age and CHA_2DS_2VASc scores). Patients with recurrent ischemic stroke had numerically lower DOAC plasma levels in our cohort. These patients tended to have a worse functional status prior to admission and were more likely to have a history of prior stroke. Propensity score matching was used to adjust for these confounders. The subgroup analysis of the different substances indicated a similar association for dabigatran and apixaban, though the analysis was hindered by low absolute numbers and requires confirmation from larger cohorts. Plasma levels of bleeding patients did not show similar results consistent with the literature[33,34] and mortality was also not associated with plasma levels as expected due to different causes of death including only one fatal ischemic stroke.

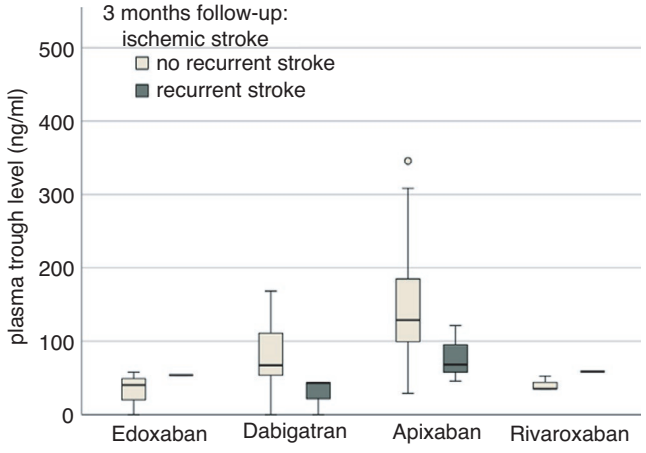

FIGURE 2 Mean plasma trough levels among patients with and without recurrent stroke despite the use of oral anticoagulation within 3 months. Mean plasma trough levels of the four different substances, stratified for ischemic stroke recurrence after propensity score matching

Despite DOAC plasma level analysis in steady state is not recommended by international guidelines,[35] the arguments for its use are continuously growing. In an Italian cohort of patients with AF and newly initiated treatment with DOAC for both primary or secondary prevention, low plasma levels were associated with thromboembolic events in 1-year follow-up in this study. The effect was more prominent among those with higher CHA_2DS_2VASc scores (median 3).[13] This is refined by our results, especially in light of the high thromboembolic risk in our cohort (median CHA_2DS_2VASc score 6). Notably, it represents the first study using plasma-level guided DOAC-treatment exclusively for secondary stroke prevention, thereby confirming the feasibility and the benefit among these vulnerable individuals.

Our study has several limitations. We report data from a monocentric cohort and the number of patients is not sufficient for proposing normative values; 15% were lost-to follow-up and could therefore not be included into the primary outcome analysis, though no major imbalances in clinically relevant parameters were detected for patients lost to follow-up. Plasma trough levels of the DOAC are pharmacodynamically substance-specific and the optimal therapeutic ranges for the four different substances remain to be determined. While trough levels in patients with stroke recurrence were numerically lower among patients on apixaban and dabigatran, our

TABLE 4 Plasma trough levels and relevant risk factors before and after propensity score matching

	Unmatched cohort			After propensity score matching	
	Recurrent stroke ($n = 10$)	No recurrent stroke ($n = 310$)		No recurrent stroke ($n = 44$)	
Age, mean (±SD) [years]	79.2 (±9.9)	78.2 (±9.4)	$p = .729$	80.3 (±8.7)	$p = .739$
Body weight, mean (±SD) [kg]	77 (±15)	79 (± 16)	$p = .758$	77 (±15)	$p = .985$
NIHSS, median (IQR)	3 (0–7.25)	3 (1–7)	$P = .643$	4.5 (1.25–7)	$P = .635$
Pre mRS, median (IQR)	2.5 (0–3)	0 (0 –2)	$P = .175$	2 (0–3)	$P = .915$
History of ischemic stroke, *n* (%)	7 (70%)	108 (34.8%)	OR: 4.364 [1.106–17.218]	29 (65.9%)	OR: 1.207 [0.272–5.351]
Arterial hypertension, *n* (%)	10 (100%)	281 (90.7%)	OR: 0.909 [0.878–0.942]	44 (100%)	-
Diabetes, *n* (%)	1 (10%)	82 (26.5%)	OR: 0.308 [0.38–2.465]	6 (13.6%)	OR: 0.704 [0.075–6.598]
Hypercholesterinemia, *n* (%)	9 (90%)	265 (85.5%)	OR: 1.528 [0.189–12.356]	38 (86.4%)	OR: 1.421 [0.152–13.325]
Heart failure, *n* (%)	5 (50%)	139 (44.8%)	OR: 1.230 [0.349–4.335]	22 (50%)	OR: 1.000 [0.253–3.948]
Plasma trough level, Mean (±SD) [ng/ml]	**58.9 (±32.4)**	**95.9. (±67.6)**	***P* = .006**	**122.2 (±95.7)**	***P* < .001**

Bold values indicates differences statistical significant.

Abbreviations: IQR, interquartile range; mRS, modified Rankin Scale; n, number; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SD, standard deviation; TIA, transient ischemic attack.

study was underpowered to show statistical significant differences for the single substances. Larger, multi-center studies should be initiated to reconfirm the results and investigate the substance-specific association. We did not perform cerebral follow-up imaging, therefore subclinical infarction was not detected.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

G. Siedler and B. Kallmünzer designed the study, analyzed and interpreted the data, and drafted the work. All authors revised the study for important intellectual content, gave final approval of the version to be published, and are accountable for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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