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# Oral Anticoagulants – A Frequent Challenge for the Emergency Management of Acute Ischemic Stroke

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**Key Words**

Oral anticoagulants · Acute ischemic stroke · Transient ischemic attack · International normalized ratio · Emergency room

**Abstract**

***Background:*** The emergency management of patients with acute ischemic stroke (IS) using oral anticoagulants (OAC) represents a great challenge. Effective anticoagulation predisposes to bleeding and represents a contraindication for systemic thrombolysis. However, patients on OAC can receive intravenous thrombolysis with recombinant tissue-type plasminogen activator if the international normalized ratio (INR) does not exceed 1.7, but data regarding the risk of hemorrhagic complications are highly controversial. Neurointerventional recanalization of intracranial artery occlusion represents an alternative option in OAC patients with acute IS. The proportion of OAC users among consecutive patients who suffer from acute IS or transient ichemic attacks (TIA) is unknown. ***Methods:*** A prospective observational study, consecutively enrolling all patients with IS or TIA admitted to our neurological emergency room (ER), was performed between August 2009 and February 2011. Basic demographic variables, present use of OAC, severity of stroke, cardiovascular risk factors, INR values and the symptom onset to presentation time were recorded. In IS patients on OAC presenting within 4.5 h after symptom onset, management was analyzed. In thrombolysed IS patients, bleeding events were documented. Outcome was assessed after 3 months. ***Results:*** During the study period, 12,237 patients were admitted to our neurological ER. IS or TIA were diagnosed in 2,074 (16.9%). Complete data were available for 1,914 of these subjects (92.3%); 53.8% were male (median age: 72 years). 69.7% suffered IS, 30.3% TIA. OAC were being used by 8.7% of all patients. OAC patients were older than non-OAC patients (78 vs. 72 years, $p < 0.001$). Subtherapeutic INR values (<2.0) were found in 67.3% of OAC patients with IS. 54.8% of all OAC IS patients presented at the ER within ≤4.5 h after the event (57/104). An INR ≤1.7 – compatible with systemic thrombolysis – was present in 33/57 patients (57.9%). Recanalization therapy was performed in 21/57 patients (36.8%). No difference in symptomatic or fatal intracerebral bleedings between thrombolysed patients with and without prior OAC use was observed ($p = 0.720$ and 0.135, respectively). Multivariable analysis of predictors of the 3-month outcome in IS

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patients revealed that prior medication with OAC was neither associated with an unfavorable clinical outcome after 3 months in the whole population of stroke patients (p = 0.235) nor in patients in whom recanalization approaches were used (n = 306; p = 0.271). ***Conclusions:*** Oral anticoagulation represents a frequent challenge for the emergency manangement of IS. A considerable proportion of anticoagulated IS patients appears to be eligible for thrombolysis. Establishing standardized treatment procedures in these patients is warranted.


## Introduction

Long-term oral anticoagulation (OAC) with vitamin K antagonists and a target international normalized ratio (INR) of 2–3 constitutes a very effective strategy for preventing stroke in patients suffering from atrial fibrillation (AF) [1–3]. Moreover, OACs are used to prevent thromboembolic events in patients with artificial heart valves [4] and for preventing recurrent deep vein thrombosis and pulmonary embolism [5, 6]. However, subtherapeutic INR levels in OAC patients are reported to be present in 24–45% in population-based studies [7–9] and at the time of stroke subtherapeutic INR values are present in 62–68% of AF patients [10, 11].

Thrombolysis with recombinant tissue-type plasminogen activator (rtPA) within a 4.5-hour time window after symptom onset is the only approved medical therapy in acute ischemic stroke (IS), although it increases the risk of brain hemorrhage [12]. The emergency management of patients with acute IS during oral anticoagulation with OAC is particularly challenging because effective anticoagulation predisposes to bleeding and represents therefore a contraindication for systemic thrombolysis.

According to current guidelines, patients on OAC can receive intravenous thrombolysis with rtPA if the INR does not exceed 1.7 [13], although data regarding the risk of hemorrhagic complications are controversial [14–19]. Neurointerventional recanalization of proximal intracranial artery occlusion represents an alternative option in OAC patients, but the available evidence regarding efficacy and safety of such procedures in general and in this particular setting is limited [20, 21].

Available studies on the prevalence of OAC at the time of an acute cerebrovascular event are based on nonconsecutive cohorts [7, 10, 19, 22], did not include transient ischemic attack (TIA) patients [7, 9–11, 17, 19, 22] or focussed exclusively on patients who underwent thrombolysis [7, 10, 11, 17, 19, 22]. A European multicenter study revealed OAC rates of about 4% in first ever stroke patients [23]. Examining changes in stroke incidence and risk factors, Rothwell et al. [24] reported a rising number of patients receiving OAC at the time of stroke between 1981 (1.1%) and 2004 (3.8%). Importantly – due to demographic changes – it is expected that the number of patients using OAC will further rise steeply. However, despite its practical importance, emergency room (ER)-based studies on the prevalence of OAC in consecutive patients with acute cerebrovascular events have not been performed to our knowledge.

The purpose of the present study was to determine the proportion of patients using OAC in a consecutive acute IS and TIA cohort in a neurological ER. We evaluated the intensity of anticoagulation at the time of the event and documented the subsequent clinical management and outcome in OAC IS patients presenting within 4.5 h after symptom onset. Furthermore, we documented bleeding events in patients treated with rtPA.

## Methods

This prospective observational study was performed in the neurological ER of the University Hospital Heidelberg. Between August 2009 and February 2011, consecutive patients who presented with acute ischemic stroke or TIA were enrolled. The catchment area of our tertiary stroke center encompasses approximately 850,000 inhabitants. Our hospital is the only provider of 24-hour/7-day acute care for stroke patients in the region. Consequently, the vast majority of patients suspected of suffering acute cerebrovascular events are primarily referred to our institution.

In the ER, a neurological examination, laboratory work and brain imaging (CT or MRI) were performed in all patients. IS and TIA were diagnosed according to current guidelines [13, 25] by neurologists experienced in stroke medicine. In ICH patients in whom evidence of secondary hemorrhages was present (i.e. hemorrhagic transformation of an infarct), a follow-up MRI in the acute phase and after 3 months was performed to differentiate between primary intracerebral hemorrhage and secondary hemorrhagic transformation.

Using a standardized questionnaire, the present use of oral anticoagulants, the medical indication for OAC therapy, basic risk factors and INR values were documented. If patients were unable to answer questions regarding the medical history or medication (e.g. aphasic patients or patients with dementia), relatives and the primary care physician were contacted. The National Institutes of Health Stroke Scale [26] was applied to measure the severity of stroke symptoms. Time from symptom onset to admission was recorded. All patients treated with rtPA received CT or MRI within 24–36 h after thrombolysis or immediately in case of clinical deterioration. Imaging was evaluated applying the SITS definitions [27] by experienced stroke neurologists and a neuroradiologist blinded to all clinical data. Neu-

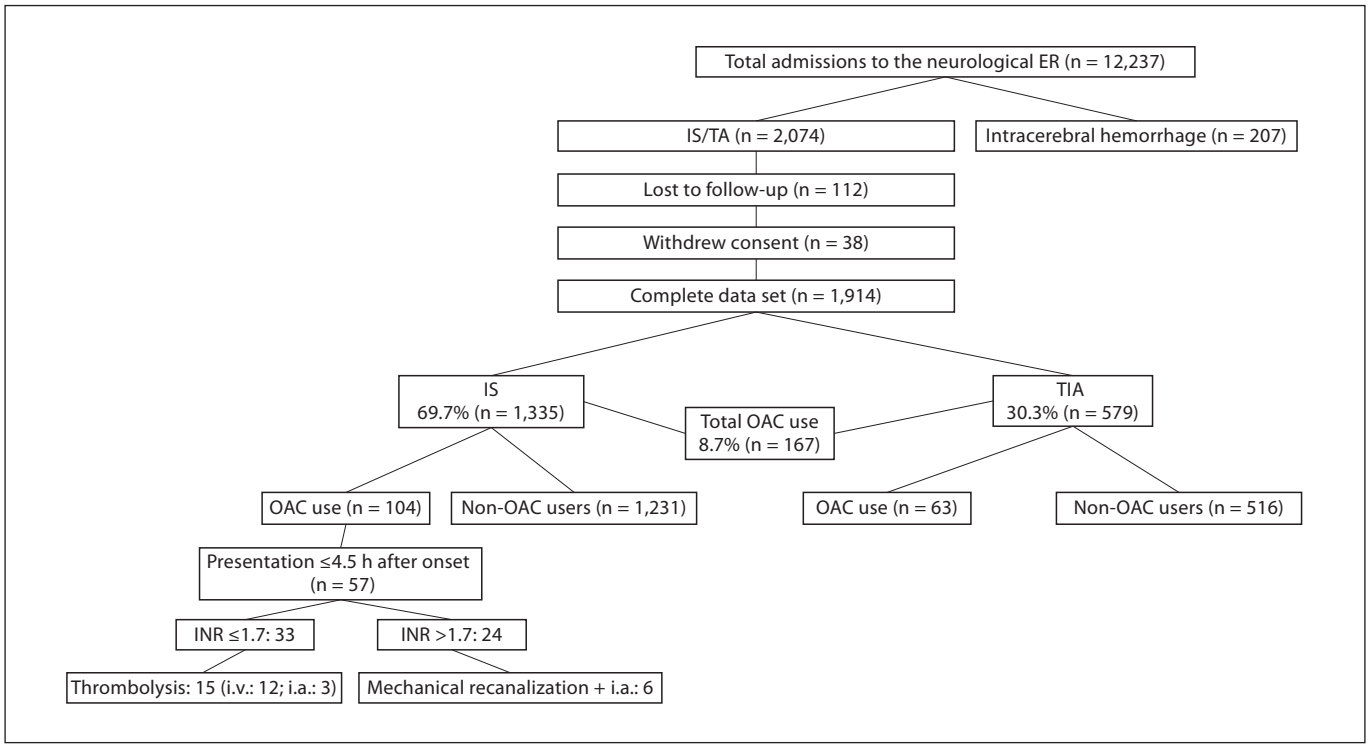


**Fig. 1.** Synopsis of the composition of our population including use of OAC and proportion of IS patients admitted within 4.5 h after onset of symptoms. n = Number of patients; i.v. = intravenous; i.a. = intra-arterial.

rological deterioration as indicated by a score on the National Institutes of Health Stroke Scale that was higher by ≥4 points than the baseline value was defined as symptomatic bleeding. Fatal bleeding was defined as in-hospital death due to intracranial bleeding after treatment with rtPA.

After 3 months, all patients or their relatives were interviewed by telephone for follow-up to assess the functional outcome using the modified Rankin scale (mRS) and standardized questions [28]. The therapeutic INR range was defined as an INR of 2–3.

The independent ethics committee of the medical faculty of the University of Heidelberg approved this study. Patients or their legal representatives gave informed consent.

*Statistical Analysis*

Most descriptive data are presented in relative frequencies, ordinal and continuous data as medians and interquartile ranges. Univariate nonparametric tests were applied to test all differences between stroke and TIA and between OAC users and non-OAC users. Additionally, binary logistic regression models were used to evaluate factors independently associated with clinical outcome after 3 months. For this purpose, the mRS was dichotomized (0–2 and 3–6). The logistic regressions were adjusted in a model for factors associated with stroke outcome (age, gender, $CHADS_2$ risk factors, medication with OAC, known AF and dichotomized initial National Institutes of Health Stroke Scale values <10 and >10, respectiveley). A two-sided p value of <0.05 was considered significant. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS 19.0).

## Results

*Population Characteristics*

Figure 1 illustrates the composition of our population. During the study period (19 months) a total of 12,237 patients were admitted to our neurological ER. Intracerebral hemorraghes were present in 207 patients (1.7%). IS or TIA were diagnosed in 2,074 of the 12,237 patients (16.9%); 3-month follow-up data were available for 92.3% (5.9% lost to follow-up; 1.8% refusal to consent). Thus, the population entered into the analysis encompassed 1,914 patients.

The majority of patients suffered an IS (69.7%, n = 1.335); TIAs were diagnosed in 30.3% (n = 579). TIA patients were significantly younger than patients with IS ($p < 0.001$; table 1).

*Differences between Anticoagulated and Nonanticoagulated Patients*

In total, 167 of our stroke/TIA population (8.7%) were using OAC at the time of admission. The predominant reason for OAC use at the time of the event was AF (n = 139). Other indications included mechanical heart valves

**Table 1.** Differences between OAC and non-OAC users

| | Non-OAC users (n = 1,747) | OAC users (n = 167) | p |
|---|---|---|---|
| Age, years | | | |
| Median | 72 | 78 | <0.001 |
| IQR | 61–80 | 71–84 | |
| Male sex, % | 53.7 | 54.5 | 0.843 |
| Stroke, % | 70.5 | 62.3 | 0.028 |
| TIA, % | 29.5 | 37.7 | 0.028 |
| Congestive heart failure, % | 9.2 | 24.0 | <0.001 |
| Arterial hypertension, % | 76.8 | 83.2 | 0.058 |
| Diabetes, % | 24.0 | 30.5 | 0.063 |
| Previous stroke/TIA, % | 23.0 | 36.5 | <0.001 |

IQR = Interquartile range.

**Table 2.** Distribution of INR values in OAC users of the entire population and risk of suffering stroke and TIA, respectively, in OAC patients in comparison with non-OAC users

| | Total OAC (n = 167) | Stroke (n = 104) | TIA (n = 63) | p |
|---|---|---|---|---|
| INR <2.0 | 101 (60.5) | 70 (67.3) | 31 (49.2) | 0.045 |
| INR ≥2.0 to ≤3.0 | 51 (30.5) | 27 (26) | 24 (38.1) | 0.621 |
| INR >3.0 | 15 (9) | 7 (6.7) | 8 (12.7) | 0.226 |

Figures in parentheses are percentages.

(15), deep vein thrombosis or recent pulmonary embolisms (7), persistent foramen ovale, hypertrophic cardiomyopathy, thrombogenic aortic arch, antiphospholipid antibody syndrome, or unidentifiable reasons (n = 6). Patients using OAC were significantly older (median age 78 vs. 72 years for non-OAC patients, $p < 0.001$) and they had more cardiovascular risk factors (table 1). Moreover, OAC users more frequently had a history of previous stroke or TIA than non-OAC users ($p < 0.001$; table 1).

*Quality of INR Control at the Time of the Event*

The median INR value in patients using OAC at the time of admission was 1.8 (1.4–2.4). The majority of stroke/TIA patients taking OAC (60.5%) had an INR <2 at presentation; 30.5% had INR values between 2.0 and 3.0, and 9% had INR values >3.0 (table 2). Subtherapeutic INR values (<2.0) were found in 67.3% of anticoagulated patients with IS and were more often observed in stroke than in TIA patients ($p = 0.045$; table 2). A previous cerebrovascular event did not predict whether INR values were within the therapeutic range ($p = 0.897$).

*Acute IS in OAC Patients*

OAC were used by 7.8% of all IS patients at the time of the event (104/1,335). The median time between symptom onset and presentation at the ER for the 104 OAC patients with IS was 3.6 h (1.6–19.8). Of these 104 patients, 57 (54.8%) presented within the time window for systemic thrombolysis (i.e. ≤4.5 h after the event; fig. 1). The median INR in OAC patients presenting within the 4.5-hour time window was 1.5 (1.2–2.2). An INR ≤1.7 – compatible with systemic thrombolysis – was present in 33/57 patients (57.9%). Consequently, 33/104 OAC patients with IS fulfilled time and coagulation criteria for systemic thrombolysis (31.7%). Systemic thrombolysis was performed in 12 of these 33 patients; 3/33 patients underwent a combined intravenous/intra-arterial procedure (fig. 1). Reasons not to intervene with systemic administration of rtPA in patients with an INR ≤1.7 encompassed age >80 years and associated severe premorbid disability (6), minor or shrinking neurological deficits (6), absent mismatch on MRI images (2), recent surgical interventions (2), seizures at symptom onset (1), neoplasias (1) or a combination of these.

Moreover, another 6 OAC stroke patients presenting within 4.5 h after symptom onset but with an INR >1.7 on admission were treated using mechanical neuroradiological recanalization approaches in combination with rtPA (fig. 1).

*Intracerebral Bleeding following Thrombolytic Therapy*

In total 320/1,335 IS patients (24.0%) were treated with rtPA; either intravenously (79.1%), intra-arterially (5.3%), by a combined intravenous/intra-arterial approach (14.4%) or by continuous intravenous rtPA infusion for 24 h (0.9%).

Of the 320 IS patients receiving thrombolysis, a CT was performed in 260 as initial brain imaging. In 22/320, an MRI was done and in 38/320 both CT and MRI were performed initially. Follow-up imaging in these 320 patients was done with CT in 257, with MRI in 25 and with both CT and MRI in 35. All OAC patients that were thrombolysed (n = 21) had CT as initial brain imaging. Follow-up imaging in the OAC patients receiving thrombolysis was done by CT in 18, by MRI in 1 and by CT and MRI in 2 patients.

**Table 3.** Predictors of 3-month outcome in IS patients (n = 1,335)

| | mRS 0–2 (n = 686) | mRS 3–6 (n = 649) | OR[1] | 95% CI | p value |
|---|---|---|---|---|---|
| Male sex | 444 (64.7) | 288 (44.4) | 0.568 | 0.438–0.737 | <0.001 |
| Age >75 years | 198 (28.9) | 403 (62.1) | 0.275 | 0.211–0.358 | <0.001 |
| Hypertension | 515 (75.1) | 536 (82.6) | 0.789 | 0.571–1.091 | 0.151 |
| Diabetes | 149 (21.7) | 199 (30.7) | 0.581 | 0.433–0.780 | <0.001 |
| Prior stroke | 150 (21.9) | 172 (26.5) | 0.724 | 0.536–0.978 | 0.035 |
| Chronic heart failure | 55 (8.0) | 96 (14.8) | 0.866 | 0.565–1.326 | 0.508 |
| OAC medication | 37 (5.4) | 67 (1.5) | 0.714 | 0.409–1.246 | 0.235 |
| Initial NIHSS >10 | 42 (6.1) | 273 (42.1) | 11.962 | 8.200–17.451 | <0.001 |
| Known AF | 84 (12.2) | 174 (26.8) | 0.940 | 0.627–1.410 | 0.766 |
| | mRS 0–2 (n = 121) | mRS 3–6 (n = 185) | OR | 95% CI | p value |
| OAC in patients who underwent recanalization approaches (n = 306) | 4 (3.3) | 17 (9.2) | 0.468 | 0.121–1.808 | 0.271 |

Outcome of IS was assessed using the mRS and was dichotomized as 0–2 and 3–6. Figures in parentheses are percentages.
[1] Model adjusted for sex, age, congestive heart failure, arterial hypertension, diabetes, prior stroke, known AF, National Institutes of Health Stroke Scale (NIHSS) scores >/<10.

Overall, any intracerebral hemorrhage according to SITS criteria (i.e. including hemorraghic transformation) after administration of rtPA occurred in 18/320 patients (5.6%; 16 in patients without and 2 in patients with prior OAC use; p = 0.33). Fatal intracerebral bleeding after thrombolysis ocurred in 10/320 patients (3.1%; without prior OAC medication: 8/290 (2.8%); with prior OAC medication: 2/21 (9.5%); p = 0.135).

*Outcome Results*

Good outcome (mRS 0–2) was less common (p = 0.001) in patients with OAC (37/104; 35.6%) than in other IS patients (649/1,231; 52.7%). Multivariable analysis of predictors of the 3-month outcome in IS patients are presented in table 3. Female sex ($p < 0.001$), higher age ($p < 0.001$), diabetes ($p < 0.001$), prior stroke events (p = 0.035) and higher initial NIHSS score ($p < 0.001$) predicted unfavorable outcome (mRS 3–6). In contrast, prior medication with OAC was neither associatd with an unfavorable clinical outcome after 3 months in the whole population of stroke patients (p = 0.235) nor in patients in whom recanalization approaches were performed (n = 306; p = 0.271).

An exploratory post hoc analysis to evaluate an impact of OAC medication on the initial NIHSS in AF IS patients of our cohort revealed that the risk of suffering a severe stroke (defined as NIHSS >10) at presentation was higher in AF IS patients who were not on OAC (OR = 2.024, 95% CI = 1.178–3.477, p = 0.011). However, we did not find an association between INR values (INR <2, 2–3 and >3) and initial NIHSS scores in OAC AF IS patients (p = 0.411).

**Table 4.** Outcome in anticoagulated and nonanticoagulated IS patients with AF and INR values

| | AF patients of the IS cohort (n = 258) | | | | |
|---|---|---|---|---|---|
| | no OAC (n = 172) | OAC yes (n = 86) | | | |
| | | INR <2 | INR 2–3 | INR >3 | total |
| mRS 0–2 | 56 (32.6) | 24 | 4 | 0 | 28 (32.6) |
| mRS 3–6 | 116 (67.4) | 41 | 14 | 3 | 58 (67.4) |
| Initial NIHSS score | | | | | |
| <10 | 87 (50.6) | 44 | 11 | 3 | 58 (67.4) |
| >10 | 85 (49.4) | 21 | 7 | 0 | 28 (32.6) |

Figures in parentheses are percentages.
NIHSS = National Institutes of Health Stroke Scale.

Moreover, we evaluated outcome at 3 months (mRS) in the IS AF patients who were anticoagulated versus those who were not anticoagulated: No association between clinical outcome and OAC status (anticoagulated vs. not anticoagulated) was present in the 258 IS AF patients (OR = 1.0; 95% CI = 0.576–1.737, p = 1.0). Moreover, no association between initial INR values and the 3-month outcome was observed (p = 0.236; table 4).

## Discussion

Our study underlines that OAC poses an important challenge for the emergency management of stroke. The major findings of our study are: (1) a substantial proportion of acute IS (7.8%) and TIA (10.9%) patients are anticoagulated at the time of the event; (2) the majority of OAC patients with cerebrovascular events have INR values below the therapeutic INR range of 2–3 established for most prophylactic indications; (3) about one third of the anticoagulated IS patients presenting inside the time window had low INR values compatible with intravenous thrombolysis; (4) overall, prior medication with OAC did not predict outcome at 3 months in IS patients, and (5) no difference in bleeding events between thrombolysed patients with and without prior OAC use was observed.

Although it is well known that patients may suffer IS despite oral anticoagulation, prospective studies consecutively enrolling acute IS patients and evaluating the impact of OAC use on stroke management in the neurological ER are sparse. Paciaroni et al. [9] reported that 4.2% of acute ischemic stroke patients used anticoagulants alone or in combination with antiplatelets at the time of hospital admission. Evaluating data from the Oxford Community Stroke Project and the Oxford Vascular Study between 1981 and 2004 revealed that the number of patients receiving OAC at the time of stroke is rising (from 1.1 to 3.8%) [24]. In contrast, about 8% of patients with an ischemic cerebrovascular event were using OAC at symptom onset in our study. Thus, orally anticoagulated IS patients represent a substantial proportion of the overall acute stroke population. Moreover, taking the aforementioned reports into account, our data may suggest that the prevalence of stroke during OAC has increased in the last decade.

The present study took place before the introduction of the new OAC which are being used by a growing number of patients. The rate of IS did not or only slightly differ between patients receiving warfarin or any of the new OAC (rivaroxaban, apixaban, dabigatran) in large clinical trials for stroke prevention in AF [29–31]. We assume that prevalence of IS patients using OAC in our study may give a good estimate of the number of IS patients under new OAC that can be expected during the course of the next few years. Prospective studies to evaluate optimal diagnostic and treatment procedures in this challenging subgroup of stroke patients are therefore urgently required.

Consistent with previous reports, the majority of OAC patients in our cohort (60.5%) were insufficiently anticoagulated (INR <2) at the time of the event: Hylek et al. [10] studied the effect of the intensity of OAC on stroke severity and mortality in a nonconsecutive cohort of patients with AF: among 188 OAC patients, 62% had INR values <2.0. O'Donnell et al. [11] evaluated preadmission medication in consecutive AF patients and reported subtherapeutic INR values in 68% of IS patients on warfarin. Accordingly, the proportion of patients with an INR below the target range is substantially higher in acute stroke patients than in patient cohorts presenting for various reasons in general ER (43%) [8].

Our finding that the risk of suffering severe strokes (NIHSS >10 at presentation) is elevated in those AF IS patients that were not on OAC is in line with the general knowledge that OAC represent an effective prevention measure to suffer severe strokes. The most likely reason why we did not observe an association between severity of stroke and INR at admission and between initial INR values and disability measured by mRS after 3 months appears to be the fact that our study was not powered for this question. To evaluate severity or outcome in AF IS patients on oral anticoagulation with therapeutic INR values versus AF patients outside therapeutic INR values or without OAC, Hylek et al. [10] included 13,559 AF patients into their study and O'Donnell et al. [11] studied a population of 948 AF IS patients. In contrast, the number of AF patients with IS in our population is only 258.

Most stroke specialists consider patients with an INR ≤1.7 to be eligible for systemic thrombolysis if therapy can be initiated within 4.5 h after symptom onset [13]. Importantly, bedside point-of-care INR measurements can accelerate thrombolysis in acute IS patients on oral anticoagulants [32]; these measurements are particularly helpful when information regarding the OAC status (e.g. aphasic patients) is not available. In our consecutive cohort, 31.7% of anticoagulated IS patients presented within 4.5 h and had INR values ≤1.7. Importantly, recanalization therapy was initiated in 36.8% of OAC IS patients presenting at the ER within 4.5 h after symptom onset.

Data on the risk of hemorrhagic complications after thrombolysis in patients with prior use of anticoagulants and outcome findings in thrombolysed OAC IS patients are still limited and indeed highly controversial [14–19]. Matute et al. [16] reported that the use of intravenous thrombolysis appears to be safe in patients previously treated with OAC with INR levels <2: 5.7% of 1,384 patients used OAC before intravenous rtPA treatment in this study; however, only data from thrombolysed patients were included into this multicenter study and no data on the overall use of OAC in stroke patients were presented. A recent observational study that used data

from the American Heart Association Get with the Guidelines Stroke Registry reports that 7.7% of acute IS patients treated with rtPA were receiving warfarin (n = 1,802/23,437); the use of intravenous tPA among warfarin patients (INR ≤1.7) was not associated with an increased risk to suffer sICH [19]. On the other hand, a recent prospective observational study suggests an increase in the risk for symptomatic intracranial and major systemic bleedings among patients that were thrombolysed and that received warfarin up to the day before stroke (n = 15/548; 2.7%) [18]. In our population, the proportion of thrombolysed stroke patients with prior OAC was 6.6% (21/320). Importantly, we did not observe differences in symptomatic or fatal intracerebral bleedings between thrombolysed patients with and without prior OAC use. In summary, these data indicate that a considerable proportion of patients who suffer acute ischemic stroke during OAC are eligible for emergency stroke treatments. The present study was not designed to particularly evaluate the efficacy of therapeutic measures in OAC stroke patients. Nonetheless, OAC did not predict outcome in our population – neither in the entire cohort nor in patients that underwent recanalization approaches.

Our study has limitations. Performance at a single tertiary stroke center may have biased our results. However, our institution is the only primary care provider for acute stroke in the region, and consecutive patient enrollment should ensure a representative character of our data. Moreover, we did not use different definitions of symptomatic hemorrhage after thrombolysis in our study, and the study was observational and treatment procedures were not prespecified limiting the assessment of effectiveness and safety of recanalization therapy in OAC patients. Adequately powered prospective studies are needed to resolve this issue.

In conclusion, our findings emphasize that OAC at the onset of acute IS represents a frequent and highly relevant problem for the emergency management of IS. Diagnostic and therapeutic measures should be established to meet this challenge.

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