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Timing of oral anticoagulation in atrial fibrillation patients after acute ischaemic stroke and outcome after 3 months: results of the multicentre Berlin Atrial Fibrillation Registry

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ABSTRACT

Background Oral anticoagulation (OAC) is key in stroke prevention in patients with atrial fibrillation (AF) but there is uncertainty regarding the optimal timing of OAC (re)initiation after stroke, as recent large randomised controlled trials have methodological weaknesses and excluded stroke patients on therapeutic anticoagulation at stroke onset as well as patients started on a vitamin K antagonist after stroke. The '1–3–6–12 days rule', based on expert consensus and referring to stroke severity, was used in clinical practice to initiate OAC after acute ischaemic stroke or transient ischaemic attack (TIA) since publication in 2013.

Methods We retrospectively assessed whether compliance to the '1–3–6–12 days rule' was associated with the composite endpoint (recurrent stroke, systemic embolism, myocardial infarction, major bleeding or all-cause death).

Results Among 708 registry patients with known AF before stroke and hospitalisation within 72 hours after stroke, 432 were anticoagulated at stroke onset. OAC was started according to the '1–3–6–12 days rule' in 255 (39.2%) patients. Non-adherence to the '1–3–6–12 days rule' was not associated with the composite endpoint within 3 months in 661 patients who (re-)started on OAC (log-rank test: p=0.74).

Results were similar for 521 patients (re)started on a non-vitamin K-dependent OAC.

Conclusion (Re)starting OAC after stroke followed the '1–3–6–12 days rule' in about 40% of all patients with AF, and more often in those anticoagulated at stroke onset. Adherence to the '1–3–6–12 days rule' did not reduce the composite clinical endpoint, if OAC was restarted within 3 months of stroke/TIA.

Trial registration number NCT02306824.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clinical decision-making regarding (re)starting oral anticoagulants (OAC) after acute ischaemic stroke or transient ischaemic attack (TIA) in atrial fibrillation (AF) patients was based on expert consensus recommendations in recent years. Recent randomised controlled studies excluded patients with therapeutic anticoagulation at stroke onset and patients restarted on a vitamin K antagonist (VKA).

WHAT THIS STUDY ADDS

⇒ In this analysis of the investigator-initiated, multicentre, prospective Berlin Atrial Fibrillation Registry, we examined the timing of the (re)initiation of OAC in a real-life stroke cohort in AF.

⇒ We assessed whether the '1–3–6–12 days rule' was associated with the composite endpoint. We demonstrate that (re)starting OAC after stroke followed the former guideline-recommended '1–3–6–12 days rule' (so-called 'Diener's Law') in about 40% of all patients. However, compliance to the '1–3–6–12 days rule' did not reduce the composite endpoint of recurrent stroke, systemic embolism, myocardial infarction, major bleeding or all-cause death within 3 months after stroke, if OAC was restarted within that time frame. Compared with the subcohort of patients (re)started on a non-vitamin K-dependent OAC (NOAC), similar results were obtained in the group (re)started on an NOAC or VKA.

INTRODUCTION

Atrial fibrillation (AF) accounts for about one out of five ischaemic strokes worldwide. Randomised controlled trials (RCTs) have demonstrated non-inferiority of non-vitamin K-dependent oral anticoagulants (NOAC) compared with the vitamin K antagonist (VKA) warfarin in (recurrent) stroke prevention in patients with non-valvular AF and at

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The analysis further emphasises the need for OAC (re)start after ischaemic stroke in AF. In addition, we observed no safety signal regarding OAC (re)start within days after stroke. Optimal timing or (re)starting OAC after stroke or TIA warrants further investigation, as compliance to the '1–3–6–12 days rule' was not linked to a clinical benefit in AF patients (re)started on OAC after stroke.

least moderate risk of stroke.[1] As NOACs are superior to warfarin by reducing the risk of intracranial bleeding, guidelines around the globe recommend NOAC use over VKA use for stroke prevention in stroke patients with AF.[1–3] However, AF patients in the acute phase of stroke were excluded from the aforementioned RCTs that led to the approval of NOACs, as there is an increased risk of haemorrhagic transformation. Subsequently, clinical decision-making regarding (re)starting OACs after acute ischaemic stroke or transient ischaemic attack (TIA) was based on expert consensus recommendations in recent years, referring to observational studies and small RCTs.[1–4] The so-called '1–3–6–12 days rule', was introduced by the European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC) in 2013 and was first adopted in principle by guidelines/consensus papers of various organisations, including the European Stroke Organisation, the EHRA and the American Heart Association/American Stroke Association (AHA/ASA).[5–8] The '1–3–6–12 days rule' is based on the assumption, that stroke severity is linked to stroke size, and stroke size is linked to the risk of haemorrhagic transformation after (re)starting OAC.[8] Therefore, this recommendation on OAC use after stroke is based on stroke severity, recommending to (re)start OAC on day 1 after TIA, on day 3 after mild stroke, day 6 after moderate stroke and day 12 after severe stroke. Recently, RCTs focusing on (re)starting OAC after stroke were published,[9–13] but final conclusions on the optimal timing of (re)starting OAC in the individual patient are pending due to methodological weaknesses.[10–13] The randomised TIMING study (Early Versus Delayed Non-Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation) was terminated early as the steering committee deemed it impossible to reach the planned sample size.[10] Furthermore, TIMING focused on NOAC starting only, using a simple time-based stratification (of ≤4 days or 5–10 days after stroke onset), excluding information on stroke severity or stroke size. In addition, the recently published randomised ELAN study (Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischemic Stroke Patients with Atrial Fibrillation) focused on NOAC starting after ischaemic stroke based on brain imaging criteria in an exploratory, hypothesis-free setting.[11] Furthermore, brain imaging was non-standardised with regard to imaging modality and timing after stroke onset. As ELAN as well as TIMING neglected information on stroke severity for bleeding risk stratification, the results of TIMING and ELAN render a comparison to the well-established '1–3–6–12 days rule' rather difficult. Of major importance, the TIMING and ELAN study excluded a substantial number of stroke patients with AF in daily clinical practice, as therapeutic anticoagulation at stroke onset as well as starting a VKA were exclusion criteria.

In our opinion, the rather vague recommendations of the ESC,[1] the AHA/ASA[7] and the European Stroke Organisation[14] regarding (re)starting (N)OAC after stroke will not change substantially, as other published RCTs like Triple AXEL[12] and AREST[13] were by far too small to impact substantially. Notably, two large RCTs (OPTIMAS, NCT02961348 and START, NCT03021928) are ongoing.[9]

As systematic prospective observational studies focusing on AF patients after acute ischaemic stroke or TIA are rare, we conducted the multicentre prospective Berlin Atrial Fibrillation Registry, including hospitalised AF patients with acute ischaemic stroke or TIA, representing an entire region in Berlin, Germany.[15 16] In the present analysis of the investigator-initiated registry, we focus on the timing of OAC prescription after acute ischaemic stroke or TIA, including AF patients anticoagulated at the time of stroke, as well as stroke patients, (re)started on a VKA. Furthermore, we report the prevalence of predefined clinical events within 3 months after the index stroke or TIA, addressing the question of whether the timing of OAC (re)start after stroke was a predictor of the composite clinical endpoint.

METHODS

Study design and study cohort

The Charité – Universitätsmedizin Berlin, Germany was the sponsor of the prospective multicentre Berlin Atrial Fibrillation Registry (NCT02306824). The design of the Berlin Atrial Fibrillation Registry was described in detail previously.[15] Patients with acute ischaemic stroke or TIA, admitted to 1 of the 16 stroke units in Berlin, Germany, were eligible for inclusion in the Berlin Atrial Fibrillation Registry if they had a history of AF or a first episode of AF in-hospital. Patients had to provide informed consent during their in-hospital stay. Confirmation of stroke or TIA was based on brain imaging and clinical criteria, following the WHO definition.[17] As no specific treatment recommendations were given to treating physicians at study sites, we are able to analyse the implementation of the '1–3–6–12 rule' in clinical practice.

In the present analysis, we excluded 336 registry patients, who were admitted to hospital later than 72 hours after onset of stroke-related symptoms, had a first episode of AF in-hospital (as this might have been detected at the end of the in-hospital stay and might be associated with rather low stroke risk)[18] or with unknown starting time of OAC (complete study cohort; figure 1). We restricted the complete study cohort to registry patients with completed 3 months follow-up information or

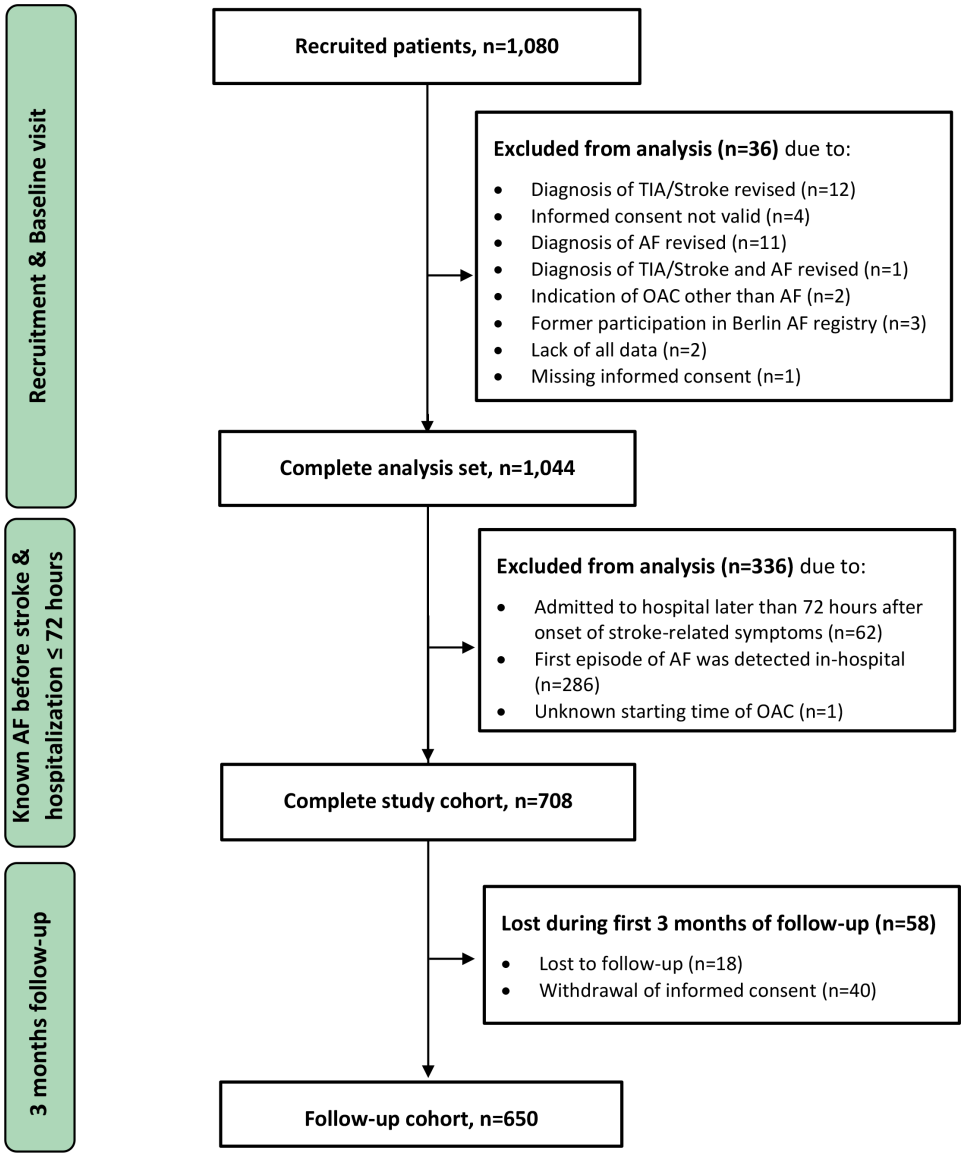

Figure 1 Derivation of the analysed cohort of Berlin Atrial Fibrillation registry patients. AF, atrial fibrillation; OAC, oral anticoagulant; TIA, transient ischaemic attack.

occurrence of recurrent ischaemic stroke, systemic embolism, myocardial infarction, haemorrhagic stroke, major bleed or all-cause death (combined endpoint) within 3 months after the index stroke/TIA (follow-up cohort; figure 1). All endpoints were adjudicated on the basis of hospital discharge letters by a Critical Event Committee (consisting of neurologists and cardiologists).[15]

Data assessment

Data assessment was described earlier in detail.[15] Medical records were analysed regarding clinical status, (re)start of OAC. The severity of the index stroke was operationally categorised into TIA, mild stroke (National Institutes of Health Scale (NIHSS) score <8 points on admission), moderate stroke (NIHSS score=8–16 points) and severe stroke (NIHSS score >16 points), for each of which a specific time point for OAC start was defined; in detail 1 day after TIA, 3 days after minor stroke, 6 days after moderate stroke and 12 days after severe stroke.[8] Infarct size was classified into three groups according to the findings of brain imaging as 'none', 'small' and 'moderate/large' infarction. Infarct size was considered 'small' if the infarct volume could be estimated to be below 25 mL, and 'moderate/large' if above 25 mL.

Arterial hypertension during the in-hospital stay of the index event was considered uncontrolled, if systolic blood pressure was ≥210 mm Hg, an intravenous antihypertensive drug was given or hypertensive crisis/uncontrolled hypertension was stated in the discharge letter. The 3 months follow-up was done centrally by telephone or postal to access medical conditions, endpoint events and medical stroke prevention. If an endpoint was reported, the treating general practitioner was contacted to obtain respective hospital discharge letters.

Application of the '1–3–6–12 days rule'

OAC prescription was considered to be 'timely (re)start' according to the '1–3–6–12 days rule', if VKA or NOAC

was (re)started on day 0 (ie, the day the index event) or on day 1 after TIA, on days 2–4 after mild stroke, days 5–7 after moderate stroke and days 11–13 after severe stroke, to apply for varying times of hospital admission. 'Early (re)start' of OAC (according to the '1–3–6–12 days rule') was defined as (re)start on day 0–1 after mild stroke, on days 0–4 after moderate stroke and on days 0–10 after severe stroke. 'Late (re)start' of OAC was defined as (re) start on day ≥2 after TIA, day >4 after mild stroke, day >7 after moderate stroke and day >13 after severe stroke.

Statistical methods

Baseline characteristics of study patients are presented as absolute and relative frequencies or median and quartiles. To compare baseline characteristics between patients with and without follow-up measures, Fisher's exact test or Wilcoxon rank sum test was performed for bivariate analyses as appropriate. To evaluate associations between patient characteristics and adherence bivariate and multiple binary logistic regression was used. ORs and respective 95% CI are reported. In addition, multivariable multinomial logistic regression was used to analyse the association between patient characteristics and different timing strategies (early, timely, late and no OAC). Additional information for the time-to-event analyses can be found in Online supplemental file. Statistical analysis was performed by using SPSS (V.29, SPSS). No adjustment for multiple testing was applied. P values have to be interpreted cautiously.

RESULTS

Study cohort

Baseline characteristics of the 708 registry patients with known AF at the time of the index stroke/TIA and hospitalisation within 72 hours of stroke onset are depicted in table 1. Median age of the 'complete study cohort' was 78 years, 47.5% were female, 30.6% had a prior stroke or TIA and the median CHA_2DS_2-VASc score before stroke was 4 (IQR 3–6) points. The CHA_2DS_2-VASc score is a point-based prediction rule to stratify the risk of stroke in AF patients; the acronym stands for congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female). The median NIHSS score on hospital admission was 2 points, 195 (27.5%) patients had a TIA as index event. Overall, 432 (61.0%) patients were anticoagulated (using NOAC or VKA) at the time of stroke/TIA, including 151 (77.4%) of 195 TIA patients and 281 (54.8%) of 513 patients with ischaemic stroke.

Within 3 months of follow-up, 58 of these 708 patients had no documented clinical endpoint (figure 1) before dropping out of the study for various reasons (listed in figure 1). Patients who dropped out had a higher prevalence of heart failure (34.5% vs 15.8%) and vascular disease (44.8% vs 31.7%), a higher CHA_2DS_2-VASc poststroke score (median, IQR: 6 (5–8) vs 6 (5–7)) compared with those remaining in the study. Despite those differences, the baseline characteristics of the remaining 650 registry patients ('follow-up cohort') were similar to patients who dropped out of the study (table 1).

(Re)starting OAC after acute ischaemic stroke or TIA

OAC (using an NOAC or VKA) was (re)started within 3 months after the index stroke/TIA in 616 (94.8%) of 650 patients with follow-up information, including 129 (19.8%) patients started on VKA and 487 (74.9%) patients on an NOAC. Median time for OAC restart was day 2 (IQR 1–5) after stroke or TIA, day 1 (IQR 0–2) after TIA and day 3 (IQR 1–6) after stroke. In other terms, 538 of 650 patients (82.8%) were (re)started on OAC within 7 days and 576 of 650 patients (88.6%) within 14 days after the index stroke/TIA, respectively. Compared with patients with (re)started OAC, patients without OAC during 3 months after the index stroke/TIA were less often anticoagulated at the time of the index stroke (20.6% vs 64.3%) and had a higher median HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly, drugs/alcohol concomitantly) score poststroke (4 vs 3 points) (online supplemental table S1).

Timing of OAC in adherence with the '1–3–6–12 days rule'

OAC (using an NOAC or VKA) was (re)started in 255 (39.2%) of 650 patients according to the '1–3–6–12 days rule' (table 2; graphic abstract), including 111 (62.0%) of 179 TIA patients, 132 (34.2%) of 386 patients with mild stroke, 11 (17.7%) of 62 patients with moderate stroke and 1 (4.3%) out of 23 patients with severe stroke. Adherence to the '1–3–6–12 days rule' was observed in 190 (47.1%) of 403 patients on OAC and in 65 (26.3%) of 247 patients without OAC at the time of stroke (table 2). Multivariable analysis, comparing (re)start in adherence versus non-adherence to the '1–3–6–12 days rule' revealed that a moderate or large infarct size (OR 2.67, 95% CI 1.09 to 6.53) versus no imaging-detected infarction and in-hospital neurological deterioration (OR 3.29, 95% CI 1.19 to 9.13) were associated with non-adherence to the '1–3–6–12 days rule' while intravenous thrombolysis (OR 0.49, 95% CI 0.26 to 0.90) and OAC intake at the time of stroke (OR 0.40, 95% CI 0.26 to 0.62) were associated with adherence to the '1–3–6–12 days rule' (table 2).

'Earlier' (re)start of OAC according to the '1–3–6–12 days rule'

OAC (using an NOAC or VKA) was (re)started earlier than recommended in 151 (23.2%) of 650 patients, including 102 (26.4%) of 386 patients with mild stroke, 31 (50.0%) of 62 patients with moderate stroke and 18 (78.3%) of 23 patients with severe stroke. Multivariable analysis, comparing earlier (re)start versus timely (re) start according to the '1–3–6–12 days rule' revealed that endovascular treatment (OR 3.74, 95% CI 1.60 to 8.73) and small infarct size (OR 2.01, 95% CI 1.27 to 3.17 vs no imaging-detected infarction) were associated with earlier

Table 1 Baseline characteristics of 708 registry patients with known AF at the time of the index stroke/TIA and hospitalisation within 72 hours of symptom onset ('complete study cohort')

	Complete study cohort n=708	Follow-up cohort n=650	Drop-outs n=58	P value
Age (years), median (IQR)	78 (72–83)	78 (71–83)	79 (73–85)	0.177
Age groups; n (%)				0.609
18–64 years	72 (10.2)	68 (10.5)	2 (6.9)	
65–74 years	167 (23.6)	155 (23.8)	12 (20.7)	
≥75 years	469 (66.2)	427 (65.7)	42 (72.4)	
Sex (male), n (%)	372 (52.5)	342 (52.6)	30 (51.7)	1.000
Index stroke: TIA, n (%)	195 (27.5)	179 (27.5)	16 (27.6)	1.000
NIHSS score on admission (points), median (IQR)	2 (1–5)	2 (1–5)	3 (1–6)	0.073
NIHSS score on admission (points), n (%)				0.666
<8 points	612 (86.4)	563 (86.6)	49 (84.5)	
8–16 points	75 (10.6)	67 (10.3)	8 (13.8)	
>16 points	21 (3.0)	20 (3.1)	1 (1.7)	
Intravenous thrombolysis, n (%)	81 (11.5)	76 (11.7)	5 (8.6)	0.666
Endovascular treatment, n (%)	51 (7.2)	48 (7.4)	3 (5.2)	0.790
Carotid endarterectomy, n (%)	7 (1)	6 (0.9)	1 (1.7)	0.452
Cardiovascular risk-factors, n (%)				
Hypertension	632 (89.3)	579 (89.1)	53 (91.4)	0.824
Heart failure	123 (17.4)	103 (15.8)	20 (34.5)	<0.001
Diabetes mellitus	222 (31.4)	199 (30.6)	23 (39.7)	0.183
Vascular disease	232 (32.8)	206 (31.7)	26 (44.8)	0.057
Prior stroke or TIA	217 (30.6)	196 (30.2)	21 (36.2)	0.373
Impaired renal function at baseline	317 (45.4)	286 (44.7)	31 (53.4)	0.217
Oral anticoagulation (baseline), n (%)	432 (61.0)	403 (62.0)	29 (50.0)	0.091
Selective serotonin reuptake inhibitor, n (%)	25 (3.6)	25 (3.9)	0 (0.0)	0.255
CHA_2DS_2-VASc post-stroke (points), median (IQR)	6 (5–7)	6 (5–7)	6 (5–8)	0.007
HAS-BLED post-stroke (points), median (IQR)	3 (3–4)	3 (3–4)	4 (3–4)	0.050
In-hospital stay (days), median (IQR)	5 (4–8)	5 (4–7)	6 (3–8)	0.909

Excluding 58 patients with incomplete 3 months follow-up information and no reported predefined clinical endpoint (recurrent ischaemic stroke, systemic embolism, myocardial infarction, haemorrhagic stroke, major bleed or all-cause death) within 3 months ('drop-outs'), the 'follow-up cohort' included 650 patients. The p value is given for the comparison of the follow-up cohort and the drop-outs.
CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly, drugs/alcohol concomitantly; NIHSS, National Institutes of Health Scale; TIA, transient ischaemic attack.

OAC (re)start while OAC intake at the time of stroke had no impact (online supplemental table S3).

'Later' (re)start of OAC according to the '1–3–6–12 days rule'

OAC (using an NOAC or VKA) was (re)started later than recommended in 210 (32.3%) of 650 patients, including 62 (34.6%) of 179 TIA patients, 133 (34.5%) of 386 patients with mild stroke, 13 (21.0%) of 62 with moderate stroke and 2 (8.7%) of 23 patients with severe stroke. Multivariable analysis, comparing later (re)start versus timely (re)start according to the '1–3–6–12 days rule' revealed that moderate or large infarct size (OR 3.87, 95% CI 1.54 to 9.74 vs no imaging-detected infarction) and in-hospital neurological deterioration (OR 3.29, 95% CI 1.07 to 10.09) were associated with later OAC (re)start while OAC intake at the time of stroke (OR 0.37, 95% CI 0.24 to 0.58) was associated with a timely OAC (re)start according to the '1–3–6–12 days rule' (online supplemental table S3).

We conducted a sensitivity analysis, in which patients who (re)started on a VKA were excluded from the analyses reported above, showing compatible results (online supplemental tables S2 and S4).

Table 2 Baseline characteristics and factors associated with non-adherence according to the '1–3–6–12 days rule'[8] in 650 registry patients with known AF at the time of the index stroke/TIA, hospitalisation within 72 hours of symptom onset and completed 3 months follow-up or predefined clinical endpoint (recurrent ischaemic stroke, systemic embolism, myocardial infarction, haemorrhagic stroke, major bleed or all-cause death) within 3 months after the index stroke/TIA

	Non-adherence n=395	Adherence n=255	Bivariate analysis* OR (95% CI)	P value	Multivariable analysis* OR (95% CI)	P value
Age, (years), median (IQR)	78 (71–84)	77 (72–82)	1.00 (0.98 to 1.01)	0.578	1.01 (0.97 to 1.05)	0.716
Sex (male), n (%)	211 (53.4)	131 (51.4)	1.09 (0.79 to 1.49)	0.610	0.81 (0.43 to 1.54)	0.523
Intravenous thrombolysis, n (%)	46 (11.7)	30 (11.8)	0.99 (0.61 to 1.62)	0.972	0.49 (0.26 to 0.90)	0.021
Endovascular treatment, n (%)	37 (9.4)	11 (4.3)	2.29 (1.15 to 4.58)	0.019	2.07 (0.91 to 4.70)	0.084
Carotid endarterectomy, n (%)	5 (1.3)	1 (0.4)	3.26 (0.38 to 28.04)	0.282	3.12 (0.34 to 28.63)	0.315
CHA_2DS_2-VASc post-stroke, median (IQR)	6 (5–7)	6 (5–6)	1.01 (0.89 to 1.14)	0.897	0.88 (0.51 to 1.49)	0.627
HAS-BLED post-stroke, median (IQR)	3 (3–4)	3 (3–4)	1.13 (0.94 to 1.36)	0.202	1.02 (0.77 to 1.37)	0.870
Infarct size according to imaging, n (%)						
None	163 (45.7)	150 (62.5)	1	<0.001	1	0.037
Small	161 (45.1)	82 (34.2)	1.81 (1.28 to 2.55)	<0.001	1.44 (0.99 to 2.10)	0.059
Moderate-to-large	33 (9.2)	8 (3.3)	3.80 (1.70 to 8.48)	0.001	2.67 (1.09 to 6.53)	0.032
Haemorrhagic transformation, n (%)	29 (7.4)	8 (3.2)	2.43 (1.09 to 5.41)	0.029	0.93 (0.36 to 2.40)	0.887
In-hospital neurological deterioration, n (%)	31 (7.8)	9 (3.5)	2.33 (1.09 to 4.98)	0.029	3.29 (1.19 to 9.13)	0.022
Uncontrolled arterial hypertension, n (%)	18 (4.6)	10 (3.9)	1.17 (0.53 to 2.58)	0.697	1.04 (0.44 to 2.46)	0.936
Oral anticoagulation on admission, n (%)	213 (53.9)	190 (74.5)	0.40 (0.28 to 0.57)	<0.001	0.40 (0.26 to 0.62)	<0.001

*Setting adherence to the '1–3–6–12 days rule' as reference. Additionally, adjusted for cardiovascular risk-factors: prior stroke or TIA, vascular disease, diabetes mellitus, hypertension, heart failure, impaired renal function at baseline.
AF, atrial fibrillation; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly, drugs/alcohol concomitantly; TIA, transient ischaemic attack.

Composite endpoint within 3 months after the index stroke/TIA

Within 3 months after the index stroke/TIA, 57 (Kaplan-Meier estimate: 9.0%, 95% CI 6.6% to 11.4%) of 708 patients (complete study cohort) reached the predefined composite endpoint (including (recurrent) ischaemic stroke (n=16) or TIA (n=15), haemorrhagic stroke (n=2; before (re)starting OAC), major bleeding (n=7), myocardial infarction (n=2), systemic embolism (n=3) or death (n=12); table 3). Information on antithrombotic therapy at the time of the clinical event is presented in online supplemental table S5. Taken together, 30 (83.3%) of 36 patients with (recurrent) ischaemic stroke or TIA, myocardial infarction or systemic embolism were on OAC or therapeutic dose heparin at the time of the ischaemic event. In addition, six (66.7%) out of nine patients with major bleeding or haemorrhagic stroke during 3 months follow-up were on OAC or therapeutic dose heparin.

As shown in the time-to-event analyses, in which 708 study patients were included (table 3), neither age nor gender (online supplemental figure S1) had a substantial effect on the frequency of the composite endpoint within 3 months. An additional analysis, in which patients were censored as soon as OAC was (re)started showed that the cumulative proportion of patients with the composite endpoint after 3 months was high in patients without OAC (31.1%, 95% CI 20.7% to 41.4%); figure 2). In patients who received OAC within 3 months, the cumulative proportion of patients with the composite endpoint after 3 months was 8.3% (95% CI 5.9% to 10.8%). Overall, the timing of the OAC (re)start was not substantially associated with the risk of the composite endpoint within 3 months in patients in whom OAC was (re)started after the index event (multivariable Cox regression: early vs timely: HR 1.17, 95% CI 0.49 to 2.78, late vs timely: HR 1.39, 95% CI 0.67 to 2.89, online supplemental table S6). In addition, the event rates for the composite endpoint within 3 months did not substantially differ between patients, in whom OAC was (re)started early, timely, or late according to the '1–3–6–12 days rule' (log-rank test: p=0.744, figure 2B). Focusing on recurrent stroke within 3 months after the index stroke/TIA, rates were similar in patients in whom OAC was (re)started early, timely or late according to the '1–3–6–12 days rule' (log-rank test: p=0.490, online supplemental figure S4). Multivariable Cox regression analysis revealed that registry patients (re)started on OAC were at lower risk for the composite endpoint compared with patients without OAC (HR 0.29, 95% CI 0.13 to 0.67, p=0.003; table 3). The interaction of the type of OAC (VKA vs NOAC) and adherence to the '1–3–6–12 days rule' was not statistically significant (online supplemental table S7). Setting (re)

Table 3 Bivariate HRs and multivariable HRs and corresponding 95% CIs on the composite endpoint (recurrent ischaemic stroke or TIA, systemic embolism, myocardial infarction, haemorrhagic stroke, major bleeding or all-cause death) according to baseline characteristics and (re)starting OAC in 708 registry patients with known AF at the time of the index stroke/TIA, hospitalisation within 72 hours of symptom onset and available start time of OAC after the index stroke/TIA

	No endpoint (n=651)	Composite endpoint (n=57)	Bivariate HR (95% CI)	Bivariate Cox-model P value	Multivariable Cox model* HR (95% CI)	Multivariable Cox model P value
Age, median (IQR)	77 (71–82)	79 (75–85)	1.03 (1.00 to 1.06)	0.077	1.00 (0.94 to 1.07)	0.966
Sex (male), n (%)	345 (53.0)	27 (47.4)	0.81 (0.48 to 1.36)	0.421	0.83 (0.29 to 2.38)	0.730
Index stroke: TIA, n (%)	180 (27.3)	15 (26.3)	0.94 (0.52 to 1.69)	0.835	1.05 (0.53 to 2.05)	0.895
NIHSS score on admission (points), median (IQR)	2 (1–5)	3 (1–5)	1.01 (0.95 to 1.07)	0.732	0.42 (0.09 to 1.94)	0.792
Intravenous thrombolysis, n (%)	78 (12.0)	3 (5.3)	0.41 (0.13 to 1.31)	0.131	0.36 (0.04 to 3.27)	0.268
Endovascular treatment, n (%)	48 (7.4)	3 (5.3)	0.69 (0.22 to 2.20)	0.527	2.73 (0.34 to 21.9)	0.363
Carotid endarterectomy, n (%)	6 (0.9)	1 (1.8)	1.84 (0.26 to 13.3)	0.546	1.01 (0.92 to 1.11)	0.344
Selective serotonin reuptake inhibitor at baseline, n (%)	23 (3.5)	2 (3.6)	0.90 (0.22 to 3.68)	0.880	0.57 (0.13 to 2.41)	0.443
CHA_2DS_2-VASc post-stroke, median (IQR)	6 (5–6)	6 (5–7)	1.20 (0.97 to 1.47)	0.088	1.13 (0.46 to 2.74)	0.792
HAS-BLED post-stroke, median (IQR)	3 (3–4)	3 (3–4)	1.26 (0.93 to 1.69)	0.135	1.08 (0.68 to 1.70)	0.756
OAC on admission	394 (60.5)	38 (66.7)	1.24 (0.72 to 2.15)	0.443	1.34 (0.68 to 2.65)	0.402
(Re-)start of OAC within 3 months follow-up	614 (94.3)	47 (82.5)	0.32 (0.16 to 0.61)	<0.001	0.29 (0.13 to 0.67)	0.003

(Re)starting of OAC was modelled as a time-varying covariate.
*Additionally adjusted for cardiovascular risk factors: prior stroke or TIA, vascular disease, diabetes mellitus, hypertension, heart failure, impaired renal function at baseline, duration of in-hospital stay (≤5 vs >5 days).
AF, atrial fibrillation; HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly, drugs/alcohol concomitantly; NIHSS, National Institutes of Health Scale; OAC, oral anticoagulant; TIA, transient ischaemic attack.

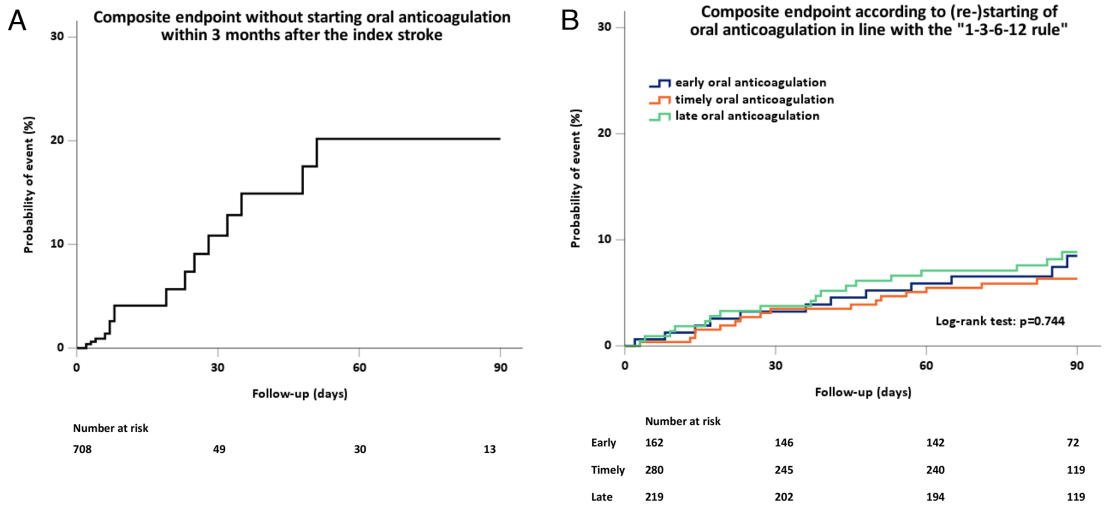

Figure 2 Kaplan-Meier curve for the probability of composite endpoint (recurrent ischaemic stroke or TIA, systemic embolism, myocardial infarction, haemorrhagic stroke, extracranial major bleed or all-cause death) within 3 months after the index stroke/TIA: (A) in registry patients without OAC after stroke, censoring patients who (re)started OAC; (B) in registry patients with (re)started OAC (early, timely or late) according to the '1–3–6–12 days rule'. Log-rank test was used to test group differences. OAC, oral anticoagulant; TIA, transient ischaemic attack.

start of OAC (online supplemental figure S2) or NOAC (online supplemental figure S3) in the individual patient as starting point, Kaplan-Meier curves demonstrate no difference regarding the composite endpoint within 3 months after stroke according to early, timely or late (re)start according to the '1–3–6–12 days rule'.

DISCUSSION

This post-hoc analysis of the multicentre prospective Berlin Atrial Fibrillation Registry revealed important findings. First, OAC was (re)started after acute ischaemic stroke or TIA in the vast majority of patients included in the registry. Notably, the incidence of major bleeding (1.1%) or haemorrhagic stroke (0.3%) was rather low in patients restarted on OAC within 3 months after stroke/TIA. This is in line with the results of the randomised TIMING[10] and ELAN[11] studies. Second, the decision to (re)start an OAC after acute ischaemic stroke or TIA was in adherence with '1–3–6–12 days rule', the standard of care at the participating centres during the registry time frame, in about 40% of all registry patients. Interestingly and not examined in TIMING[10] or ELAN[11] studies, resumption of OAC in anticoagulated AF patients at the time of stroke more often conformed to the '1–3–6–12 days rule' than in non-anticoagulated AF patients at the time of stroke. Third, 'early' (re)start of OAC (vs (re)start according to the '1–3–6–12 days rule') was present in about one out of four registry patients, and 'late' (re)start of OAC was observed in about one out of three registry patients. Fourth and of major importance, the composite of recurrent stroke, systemic embolism, myocardial infarction, major bleeding or all-cause death within 3 months after the index stroke was not associated with adherence to the '1–3–6–12 days rule'. As the composite endpoint was rather low within the first 3 months (Kaplan-Meier estimate: 9.0%, 95% CI 6.6% to 11.4%) and the vast majority of patients were (re)started on OAC, adherence to the '1–3–6–12 days rule' did not impact on the composite endpoint.

In addition, OAC (re)start resulted in a fourfold decrease in the cumulative probability of the combined endpoint. Patients who were not treated with an OAC during follow-up were less likely to be anticoagulated at the time of stroke, had a higher HAS-BLED score and more often had a neurological deterioration while in hospital. Fifth, excluding registry patients (re)started on a VKA, NOAC (re)starting resulted in similar findings regarding the composite endpoint with slightly varying impact factors for (non-)adherence to the '1–3–6–12 days rule'.

Of note, the Berlin Atrial Fibrillation Registry was designed to address adherence to the '1–3–6–12 days rule' in clinical practice while published and awaited (prospective) observational studies and RCTs focused on (re)starting OAC according to selected time periods after stroke or on brain imaging findings.[4 10 11 19–21] Our findings are in line with a recent retrospective analysis from Taiwan's National Health Insurance Research Database that compared early versus delayed (re)starting of OAC after acute ischaemic stroke according to the '1–3–6–12 days rule' without detecting differences regarding the composite of the efficacy or safety outcomes.[19] To assess adherence to the '1–3–6–12 days rule', clinical stroke severity and infarct size had to be considered in addition to the time period after stroke onset.[5] Moreover, serious adverse events were prospectively assessed and adjudicated by a critical event committee in the Berlin Atrial Fibrillation Registry, which is a standard not met in previous observational studies.[19 22–29]

However, the following limitations have to be addressed. First, providing informed consent by all registry patients implies a selection bias towards patients with less severe stroke. Second, we cannot exclude that undocumented factors may have influenced the physicians' choice of medical stroke prevention in an individual patient. Third, stroke severity was defined according to the NIHSS score on admission but alterations of the NIHSS score are observed in the acute phase of stroke and especially in patients undergoing thrombolysis and/or endovascular treatment. Fourth, despite covering the entire Berlin area, the generalisability of the results is limited to non-European countries. Fifth, the number of AF patients without (re) starting OAC after stroke/TIA is limited in the Berlin Atrial Fibrillation Registry.

CONCLUSIONS

(Re)starting OAC after stroke follows the '1–3–6–12 day rule', as recommended in guidelines at the time of enrolment, in about 40% of all registry patients. Notably, non-adherence to the '1–3–6–12 days rule' was not associated with a higher rate of the composite clinical endpoint, if OAC was (re)started within 3 months after stroke/TIA. Our findings are in line with recent RCTs indicating that OAC start within the first 2 weeks after ischaemic stroke or TIA is safe in selected patients. Furthermore, we provide valuable information on OAC restart and OAC start using VKA, which is beyond the scope of recent RCTs.

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REFERENCES

1 Hindricks G, Potpara T, Dagres N, *et al*. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of

Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021;42:373–498.
2 Joglar JA, Chung MK, Armbruster AL, *et al*. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2024;149:e1–156.
3 Steffel J, Heidbüchel H. 2021 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: comment-Authors' reply. *Europace* 2021;23:1685–6.
4 Palaiodimou L, Stefanou M-I, Katsanos AH, *et al*. Early Anticoagulation in Patients with Acute Ischemic Stroke Due to Atrial Fibrillation: A Systematic Review and Meta-Analysis. *J Clin Med* 2022;11:4981.
5 Kirchhof P, Benussi S, Kotecha D, *et al*. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;18:1609–78.
6 Steffel J, Verhamme P, Potpara TS, *et al*. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Eur Heart J* 2018;39:1330–93.
7 Kleindorfer DO, Towfighi A, Chaturvedi S, *et al*. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. *Stroke* 2021;52:e364–467.
8 Heidbuchel H, Verhamme P, Alings M, *et al*. European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2013;15:625–51.
9 Seiffge DJ, Werring DJ, Paciaroni M, *et al*. Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation. *Lancet Neurol* 2019;18:117–26.
10 Oldgren J, Åsberg S, Hijazi Z, *et al*. Early Versus Delayed Non-Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING): A Registry-Based Randomized Controlled Noninferiority Study. *Circulation* 2022;146:1056–66.
11 Fischer U, Koga M, Strbian D, *et al*. Early versus Later Anticoagulation for Stroke with Atrial Fibrillation. *N Engl J Med* 2023;388:2411–21.
12 Hong K-S, Kwon SU, Lee SH, *et al*. Rivaroxaban vs Warfarin Sodium in the Ultra-Early Period After Atrial Fibrillation-Related Mild Ischemic Stroke: A Randomized Clinical Trial. *JAMA Neurol* 2017;74:1206–15.
13 Labovitz AJ, Rose DZ, Fradley MG, *et al*. Early Apixaban Use Following Stroke in Patients With Atrial Fibrillation: Results of the AREST Trial. *Stroke* 2021;52:1164–71.
14 Klijn CJ, Paciaroni M, Berge E, *et al*. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. *Eur Stroke J* 2019;4:198–223.
15 Haeusler KG, Tütüncü S, Kunze C, *et al*. Oral anticoagulation in patients with atrial fibrillation and acute ischaemic stroke: design and baseline data of the prospective multicentre Berlin Atrial Fibrillation Registry. *Europace* 2019;21:1621–32.
16 Tütüncü S, Olma M, Kunze C, *et al*. Off-label-dosing of non-vitamin K-dependent oral antagonists in AF patients before and after stroke: results of the prospective multicenter Berlin Atrial Fibrillation Registry. *J Neurol* 2022;269:470–80.
17 Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull World Health Organ* 1976;54:541–53.
18 Sposato LA, Lip GYH, Haeusler KG. Atrial fibrillation first detected after stroke: is timing and detection intensity relevant for stroke risk? *Eur Heart J* 2024;45:396–8.
19 Chang PY, Wang WT, Wu WL, *et al*. Oral Anticoagulation Timing in Patients with Acute Ischemic Stroke and Atrial Fibrillation. *Thromb Haemost* 2022;122:939–50.
20 King BT, Lawrence PD, Milling TJ, *et al*. Optimal delay time to initiate anticoagulation after ischemic stroke in atrial fibrillation (START): Methodology of a pragmatic, response-adaptive, prospective randomized clinical trial. *Int J Stroke* 2019;14:977–82.
21 Best JG, Arram L, Ahmed N, *et al*. Optimal timing of anticoagulation after acute ischemic stroke with atrial fibrillation (OPTIMAS): Protocol for a randomized controlled trial. *Int J Stroke* 2022;17:583–9.
22 Paciaroni M, Agnelli G, Falocci N, *et al*. Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation: Effect of Anticoagulation and Its Timing: The RAF Study. *Stroke* 2015;46:2175–82.
23 Paciaroni M, Agnelli G, Falocci N, *et al*. Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin-K Oral Anticoagulants (RAF-NOACs) Study. *J Am Heart Assoc* 2017;6:e007034.
24 Arihiro S, Todo K, Koga M, *et al*. Three-month risk-benefit profile of anticoagulation after stroke with atrial fibrillation: The SAMURAI-Nonvalvular Atrial Fibrillation (NVAF) study. *Int J Stroke* 2016;11:565–74.
25 Seiffge DJ, Traenka C, Polymeris A, *et al*. Early start of DOAC after ischemic stroke: Risk of intracranial hemorrhage and recurrent events. *Neurology (ECronicon)* 2016;87:1856–62.
26 Macha K, Volbers B, Bobinger T, *et al*. Early Initiation of Anticoagulation with Direct Oral Anticoagulants in Patients after Transient Ischemic Attack or Ischemic Stroke. *J Stroke Cerebrovasc Dis* 2016;25:2317–21.
27 Cappellari M, Carletti M, Danese A, *et al*. Early introduction of direct oral anticoagulants in cardioembolic stroke patients with non-valvular atrial fibrillation. *J Thromb Thrombolysis* 2016;42:393–8.
28 Gioia LC, Kate M, Sivakumar L, *et al*. Early Rivaroxaban Use After Cardioembolic Stroke May Not Result in Hemorrhagic Transformation: A Prospective Magnetic Resonance Imaging Study. *Stroke* 2016;47:1917–9.
29 Deguchi I, Tanahashi N, Takao M. Timing of Treatment Initiation With Oral Anticoagulants for Acute Ischemic Stroke in Patients With Nonvalvular Atrial Fibrillation. *Circ J* 2017;81:180–4.