Cognitive Impairment Is Not a Predictor of Failure to Adhere to Anticoagulation of Stroke Patients with Atrial Fibrillation

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Key Words

Oral anticoagulation · New oral anticoagulants · Dementia · Ischemic stroke · Drug adherence

Abstract

Background: Oral anticoagulation (OAC) with vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC) is an effective strategy that is used for stroke prevention in patients with atrial fibrillation (AF). However, OAC is underused particularly in elderly patients, who are often physically disabled or cognitively impaired. We aimed at evaluating the effect of cognitive status and disability on OAC adherence 1 year after stroke or TIA. **Methods:** In this prospective, single-center, observational study patients with ischemic stroke or TIA were consecutively included between 3/2011 and 9/2012. The detailed medical history, basic demographic variables, cardiovascular risk factors, stroke severity according to the National Institutes of Health Stroke Scale (NIHSS), medication including OAC were all recorded. Cognitive performance was measured using the Montreal Cognitive Assessment (MoCA) score at baseline. The functional status was assessed by recording activities and instrumental activities of daily living, respectively (ADL, IADL). After 12 months, patients had a follow-up visit to reassess the cognitive and functional status (MoCA, ADL and IADL) and to document the current use of

OAC. **Results:** In total, 12 months after the ischemic stroke or TIA AF had been diagnosed in 160/586 (27.3%). Of these, 151 patients (94.4%) were treated with OAC. OAC was performed using VKA in 79/151 (52.3%) and DOACs in 72/151 (47.7%). Cognitive impairment at 12 months follow-up was not associated with the absence of OAC treatment. However, regression analysis revealed that patients with AF with physical (ADL) and functional disability (IADL) were less likely to be treated with OAC ($p = 0.08$ and $p = 0.04$, respectively) 12 months after a stroke. None of these two factors, however, was independently associated with nonadherence to OAC 12 months after stroke. Although cognitive performance was similar in patients receiving VKA and direct anticoagulants (DOAC), adherence to VKA tended to be lower (82.6 vs. 94.6%, $p = 0.12$). **Conclusions:** In stroke and TIA patients with AF, the multifactorial medical and functional constellation rather than cognitive impairment specifically can be an obstacle for long-term OAC.

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Introduction

Oral anticoagulation (OAC) with vitamin K antagonists (VKA) or direct oral anticoagulants (DOAC) is a strategy that is used for stroke prevention in patients with

atrial fibrillation (AF) [1–4]. Nevertheless, OACs are substantially underused in patients with AF [5] because of undesirable properties of VKA [6, 7]. Anticoagulation with VKA is a particular challenge in the elderly because of a higher risk of bleeding complications and the need of coagulation monitoring. However, elderly patients with AF are at a higher risk of ischemic strokes and therefore they benefit most from OAC [8].

Rates of adherence to OAC 1 year after stroke ranged from 78 to 89% in previous studies [9, 10] exceeding those in primary prevention [11]. Nevertheless, cognitive impairment, a frequent comorbidity in the elderly may challenge adequate OAC. Data about the influence of cognitive impairment to OAC adherence are limited. In a prospective study conducted in a department of internal medicine, cognitive impairment was an independent predictor of not receiving OAC at hospital discharge [12].

DOAC are at least as effective in stroke prevention as VKA [1–4] and bleeding complications are significantly reduced. DOAC can be prescribed with a fixed dose. This may facilitate the handling of OAC. No data are available regarding the role of cognitive impairment on adherence to DOAC in secondary prevention.

The primary aim of our observational study was to analyze drug adherence to OAC (DOAC and VKA) 12 months after acute ischemic stroke or TIA. We focused on the impact of cognitive impairment on long-term anticoagulation in AF.

Methods

This prospective observational study enrolled consecutive stroke and TIA patients between 03/2011 and 09/2012. Diagnosis of ischemic stroke or TIA was made by experienced stroke physicians in accordance with current guidelines [13].

The routine work-up encompassed assessment of the National Institute of Stroke Scale (NIHSS) and the premorbid modified Rankin Scale Score (mRS). Using a standardized questionnaire, we recorded the detailed medical history and basic demographic variables. In particular, we focused on premorbid OAC treatment and OAC treatment at discharge. Moreover, we documented the current residential status (e.g. independent alone, special-care home). Cognitive performance was measured using the Montreal Cognitive Assessment (MoCA) within the first days of admission (median 2 days after admission) [14]. In accordance to the original publication of the test, a MoCA score of <26 was defined as cognitively impaired [14]. To adjust for lower educational status, 1 point of the MoCA scale was added for less than 12 years of education [14]. Premorbid functional status was measured by means of the activities and the instrumental activities of daily living (ADL, IADL) before the stroke [15, 16]. Both scales were considered normal if no impairment was present. After 12 months, patients had a follow-up visit to reassess the cognitive and functional status

(MoCA, ADL and IADL) and to document the current use of OAC.

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

Statistical Analysis

Data description is performed using absolute and relative frequencies for categorical variables and means and standard deviations for continuous variables. Patient's characteristics were compared using the Student's t-test for continuous variables, the Mann-Whitney U test for ordinaly-scaled variables, and the χ^2 test for categorical variables. In patients with AF, univariable logistic regression was used to evaluate factors associated with the absence of OAC treatment (VKA and DOAC) after 12 months. In addition to the MoCA cut-off <26, we performed a post-hoc sensitivity analysis for an MoCA cut-off <22 as suggested by a reviewer. The multivariable logistic regression analysis was used to determine factors independently associated with the use of OAC. All variables with $p \leq 0.1$ in univariable logistic regression were included (table 3).

Results

Population Characteristics

Figure 1 illustrates the composition of the study population. Table 2 presents characteristics of patients at baseline and after 12 months. In total, 160 of 586 (27.3%) patients with follow-up assessment had AF ($n = 127$ at discharge, 33 new diagnoses during follow-up).

There were significant differences between patients with and without follow-up visit (table 1).

Adherence to Oral Anticoagulation

After 12 months, 94.4% of patients with AF were anticoagulated (table 2). Physician-stated reasons for failure to anticoagulate were risk of falls ($n = 2$) and previous bleeding complications ($n = 5$). In 2 patients, OAC had not been started despite recommendation. VKA was used in 79/151 (52.3%) and DOACs in 72/151 (47.7%). Patients treated with DOACs (74.7 ± 5.6) were significantly older compared to VKA (71.2 ± 11.3). However, there was no significant difference in terms of cognitive performance (table 4).

Adherence to DOAC tended to be higher compared to VKA-adherence. Of 46 AF patients treated with VKA at discharge, 38 (82.6%) were still taking VKA after 12 months (3 stopped OAC and 5 switched to NOACs). 53/56 (94.6%) patients initially treated with DOACs were still taking DOACs after 12 months. After adjustment for age there was no significant difference ($p = 0.12$) between VKA and DOAC.

Fig. 1. Flow diagram of the study population. * Insufficient German language abilities (48), major physical disability (10) or schizophrenic disorder (1).

MoCA Performance, Activity of Daily Living and Instrumental Activity of Daily Living

After 12 months, cognitive performance was significantly better compared to baseline (median MoCA score: 24 IQR 20/27 vs. 25 IQR 22/28, $p = 0.001$). There were significantly less patients with cognitive impairment (MoCA <26) at 12-months follow-up compared to baseline evaluation (49.0 vs. 58.7%, $p = 0.001$). ADL and IADL scores differed significantly at the 12-month follow-up visit compared to baseline evaluation (table 2).

Predictive Parameters for Absence of Oral Anticoagulation 12 Months after Stroke

Univariable regression with data from 12-month revealed lower scores for the ADL ($p = 0.08$) and IADL ($p = 0.04$) as predictive factors for the absence of OAC 12 months after the stroke (table 3). None of the two variables was an independent predictor for the absence of OAC 12 months after stroke.

Discussion

Our study revealed that (1) 12 months after acute stroke, the vast majority of AF patients were treated with OAC. (2) Physical and functional disabilities rather than cognitive performance were associated with the absence of OAC after 12 months. (3) Long-term adherence to OAC tended to be higher in patients treated with DOAC compared to VKA.

Rates of long-term adherence to OAC were consistently higher in previous studies of secondary compared to primary stroke prevention [11]. Nevertheless, long-term anticoagulation is frequently not started or continued especially in elderly stroke patients in reality [5, 17]. Our study on OAC adherence showed a higher rate of 94.4% of drug adherence one year after stroke than previously described (78–89%) [9, 10]. This might be explained by the younger age of AF patients in our study (mean 72.9 vs. 75.3 years). Because of a higher rate of bleeding

Table 1. Patients characteristics

Data	All patients (n = 990)	Patients with FU (n = 586)	Patients without FU (n = 404)	p value
<i>Demographic features</i>				
Age	67.2±12.3	67.2±12.7	68.5±14.1	0.12*
Male	618 (62.4)	377 (64.3)	241 (59.7)	0.14***
Education level ≤12 years	607 (61.3)	340 (58.0)	267 (66.1)	0.002***
Living status				
Independent	890 (89.9)	554 (94.5)	340 (84.2)	0.002***
Special-care-home	100 (10.1)	32 (5.5)	38 (9.4)	0.002***
<i>Cardiovascular risk factors</i>				
Hypertension	837 (84.5)	489 (83.4)	348 (86.1)	0.25***
Diabetes mellitus	248 (25.1)	134 (22.9)	114 (28.2)	0.06***
Vascular	226 (22.8)	129 (22.0)	97 (24.0)	0.46***
Smoking	232 (23.4)	131 (22.4)	101 (25.0)	0.33***
<i>Medical history</i>				
AF	218 (22.0)	127 (21.7)	91 (22.5)	0.75***
Previous stroke				
Ischemic	268 (27.1)	158 (27.0)	110 (27.2)	0.93***
Hemorrhagic	14 (1.4)	10 (1.7)	4 (1.0)	0.35***
<i>Treatment before admission</i>				
Oral anticoagulation	85 (8.6)	45 (7.8)	34 (8.4)	0.87***
Antiplatelet therapy	369 (37.3)	235 (40.1)	183 (45.3)	0.10***
<i>Stroke characteristics</i>				
Ischemic stroke	749 (75.7)	432 (73.7)	317 (78.5)	0.09***
TIA	241 (24.3)	154 (26.3)	87 (21.5)	0.09***
NIHSS at baseline (median, IQR)	3 (1/6)	2 (0/5)	3 (1/7)	0.001**
pmRS at baseline (median, IQR)	0 (0/1)	0 (0/1)	0 (0/2)	0.001**
<i>Neuropsychological assessment</i>				
MoCA (median IQR)	23 (19/26)	24 (20/27)	22 (18/26)	0.001**
ADL (median IQR)	6 (6/6)	6 (6/6)	6 (6/6)	0.001**
IADL (median IQR)	24 (22/24)	24 (23/24)	24 (21/24)	0.001**

Values in round brackets denote percentages or standard deviations, respectively.

AF = Atrial fibrillation; TIA = transient ischemic attack; NIHSS = National Institute of Health Stroke Scale; MoCA = montreal cognitive assessment; ADL = activity of daily living; IADL = instrumental activity of daily living; IQR = interquartile range.

* Student's t-test, ** Mann-Whitney U test, *** χ^2 test.

complications, elderly patients less frequently receive OAC [8]. Toward the end of our study, DOACs were approved for their use in stroke prevention in AF with their advantage of lower rates of intracranial bleedings and the use of a fixed dose [18]. This favorable safety profile of DOACs might have influenced adherence rates especially in elderly patients.

Oral anticoagulation in particular with VKA requires a high degree of compliance that cognitively impaired patients cannot easily afford. Previous reports on geriatric and medical patients revealed associations of OAC

adherence and cognitive status [19, 20]. Moreover, cognitive impairment was associated with a worse quality of OAC measured by the time in therapeutic range [19, 21, 22]. In contrast, our study of stroke patients showed that reduced levels in physical (ADL) and functional (IADL) abilities rather than cognitive impairment (MoCA <26) were associated with OAC nonadherence after 12 months. As test accuracy was shown to be only moderate with a cut-off <26, we did the same analysis with a cut-off <22 [23]. This yielded very similar results as our previous analysis. Apart from different study populations (medi-

Table 2. Characteristics of patients with 12 month follow-up examination including MoCA evaluation (n = 586)

	Baseline	12-months FU	p value
<i>Demographic features</i>			
Living status			
Independent	554 (94.5)	484 (82.6)	0.001*
Special-care-home	32 (5.5)	49 (8.4)	0.001*
<i>Medical history</i>			
Stroke during FU			
Ischemic	–	16 (2.7)	
TIA	–	11 (1.9)	
OAC			
OAC before index stroke/TIA	45 (7.8)	–	
Treatment with OAC	102 (17.4)	151 (25.8)	0.001*
Treatment with			
VKA	46/102 (45.1)	79/151 (52.3)	
DOAC	56/102 (54.9)	82/151 (47.7)	
<i>Stroke characteristics</i>			
NIHSS (median IQR)	2 (0/5)	0 (0/1.5)	0.001***
<i>Neuropsychological assessment</i>			
MoCA (median IQR)	24 (20/27)	25 (22/28)	0.001***
ADL (median IQR)	6 (6/6)	6 (6/6)	0.001***
IADL (median IQR)	24 (23/24)	24 (20/24)	0.001***

Values in round brackets denote percentages or standard deviations, respectively.

FU = Follow-up; TIA = transient ischemic attack; OAC = oral anticoagulation; VKA = vitamin k antagonist; DOAC = direct oral anticoagulation; MoCA = Montreal cognitive assessment; ADL = activity of daily living; IADL = instrumental activity of daily living. * McNemar test, ** paired Student's t-test, *** Wilcoxon paired test.

Table 3. Predictive values for the absence of oral anticoagulation 12 months after stroke in AF patients

	Univariate			Multivariate		
	OR	p value	95% CI	OR	p value	95% CI
Age	1.05	0.26	0.96–1.14			
MoCA <26 vs. MoCA ≥26	4.97	0.14	0.60–41.40			
MoCA <22 vs. MoCA ≥22	1.66	0.50	0.38–7.28			
ADL 12 months	3.37	0.08	0.85–13.37	1.45	0.73	0.17–12.59
IADL 12 months	0.87	0.04	1.77–0.99	0.90	0.27	0.74–1.09
Living status 12 months*	1.73	0.52	0.33–9.08			
NIHSS 12 months	1.23	0.15	0.93–1.64			

ADL = Dichotomized activity of daily living 1–4 and 5–6; IADL = instrumental activity of daily living; NIHSS = National Institute of Health Stroke Scale.

Patients with OAC: n = 151, patients without OAC: n = 9.

cal and geriatric patients vs. stroke patients) this might be explained by the older study population in previous reports compared to ours (mean age 81.7 vs. 72.9 years), as prevalence of cognitive impairment increases with age. Consistent with our results Tanislav and coworkers

found that not only cognitive status but also worsening disability is associated with OAC treatment after stroke [17].

DOACs might represent a good alternative to VKA. We observed higher adherence rates of DOACs (94.6%)

Table 4. Differences between 12-month follow-up in AF patients with OAC treatment comparing VKA and DOACs

Data	AF patients with			p value
	OAC (n = 151)	VKA (n = 79)	DOAC (n = 72)	
Demographic features				
Age	72.9±9.7	71.2±11.3	74.7±5.6	0.03*
Male	94 (62.3)	51 (64.6)	47 (65.3)	0.46***
Education level ≤12 years	98 (64.9)	51 (64.6)	47 (65.3)	0.74***
Cardiovascular risk factors				
Hypertension	136 (90.1)	72 (91.1)	64 (88.9)	0.65***
Diabetes mellitus	40 (26.7)	23 (29.1)	17 (23.6)	0.45***
Stroke characteristics				
Ischemic stroke	121 (80.1)	61 (77.2)	60 (83.3)	0.35***
NIHSS at baseline (median IQR)	1 (0/2)	0 (0/2)	1 (0/2)	0.86**
Neuropsychological assessment				
MoCA (median IQR)	25 (21/27)	24 (21/27)	25 (22/26)	0.90**
ADL (median IQR)	6 (5/6)	6 (5/6)	6 (5/6)	0.20**
IADL (median IQR)	23 (18.5/24)	22 (18.5/24)	23 (18/27)	0.60**

Values in round brackets denote percentages or standard deviations, respectively.

VKA = Vitamin K antagonist; OAC = oral anticoagulation; DOAC = direct oral anticoagulation; NIHSS = National Institute of Stroke Scale; MoCA= Montreal cognitive assessment; ADL = activity of daily living; IADL = instrumental activity of daily living.

* Student's t-test, ** Mann-Whitney U test, *** χ^2 test.

compared to VKAs (82.6%) one year after stroke. However, this difference was not significant even after age adjustment as patients treated with DOACs were significantly older compared to VKA-treated patients in our cohort. Interestingly, a previous study showed contradicting results regarding age difference between DOAC and VKA patients [24]. The older age of DOAC treated patients in our cohort might reflect the prescription of DOACs particularly in elderly patients with a higher risk of bleeding complications, as DOACs were associated with a lower risk of intracerebral hemorrhages [1–3]. Although DOACs have overcome most inconveniences related to VKA indirect evidence from the largest AF, RCTs have shown adherence rates to DOACs that were lower compared to VKA [1–3]. However, these data cannot be transferred to DOAC use in clinical practice, because in RCTs regular follow-up visits with coagulation control increase drug adherence of OAC, and one major factor influencing drug adherence of DOACs in the real-world setting is the lacking necessity of regular coagulation monitoring [25].

Our study had strengths and limitations. It was a consecutively and prospectively recruiting study. The single-center design may prevent us from generalizing our

results. However, our center is the only provider of acute care for stroke patients within the region. A limitation of our study was the selection bias of our follow-up-cohort, which was significantly younger, less affected by their strokes and which had significantly better cognitive function. Furthermore, we did not record times in therapeutic range values to evaluate the quality of OAC treatment.

In conclusion, one year after stroke the vast majority of patients with AF are anticoagulated no matter how OAC was performed – with VKA or with DOACs. A multifactorial medical and functional constellation rather than specifically cognitive impairment can be an obstacle for OAC adherence in stroke patients.

Disclosure Statement

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