Impact of prior oral anticoagulation on admission stroke severity in patients with atrial fibrillation

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Background and Aims. In patients with atrial fibrillation, oral anticoagulation therapy is indicated for both primary and secondary prevention of stroke/systemic embolism. Though direct oral anticoagulants with greater safety and efficacy than warfarin were introduced into clinical practice at the beginning of the last decade, even now not all patients with AF have adequate preventative anticoagulant treatment. The primary goal of this study was to evaluate the impact of prior use of oral anticoagulants on admission stroke severity in those with AF. Other aims were, *inter alia*, to assess the trend in atrial fibrillation prevalence in the years of the HISTORY trials 2012–2021 carried out in the Czech Republic and use of oral anticoagulants (OAC) in ischemic stroke (IS) patients.

Methods. We analyzed consecutive ischemic stroke patients who had been enrolled in the HISTORY (Heart and Ischemic STrOke Relationship studY) study registered on ClinicalTrials.gov (identifier NCT01541163) in the year 2012 and carried out a yearly comparison (detailed in the text).

Results. In total, there were 1059 patients (55.9% males, mean age 71.7±12.8). There was no significant difference over the time period in rate of known (18.3 vs. 16.5%, *P*=0.442) or newly detected AF (17.0 vs. 16.0%, *P*=0.665), but sigificantly more patients with known AF were treated with oral anticoagulants before IS in the year 2021 (32.1 vs. 70.7%, *P*<0.0001), and direct oral anticoagulants (3.6 vs. 35.4%, *P*<0.0001). The number of patients with atrial fibrillation had not changed significantly over the years (26.2 vs. 31.3%). Patients on OAC had a lower median admission score on the National Institutes of Health Stroke Scale (NIHSS) than those not using an oral anticoagulant (6 vs. 16, *P*=0.0004) in 2021.

Conclusions. There was no significant upward trend in atrial fibrillation in stroke patients admitted between 2012 and 2021, but patients with known AF were significantly more frequently treated with oral anticoagulants and direct oral anticoagulants (DOAC) in 2021. Patients on OAC had lower admission NIHSS scores than those not using any anticoagulent in the year 2021. The difference in the median admission NIHSS between the patients on OAC and those without OAC treatment was not significant in the year 2012 (6 vs. 12, *P*=0.066). This might be related to the fact that substantially fewer patients in 2012 were on DOACs, which are considered more effective than warfarin.

Key words: ischemic stroke, atrial fibrillation, oral anticoagulation, direct oral anticoagulants, stroke severity

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INTRODUCTION

Cardioembolism is emerging as the second most common etiological subtype of ischemic stroke (IS) following the cryptogenic subtype[1]. However, some cryptogenic ISs are caused by undetected cardioembolism[1]. Atrial fibrillation (AF) is the most frequent cause of cardioembolic IS (ref.[1,2]). It is the most common arrhythmia in adult populations and the prevalence increases substantially with age, so that in people over 80 years, the prevalence is around 20% (ref.[1,3-5]). AF usually occurs in paroxysmal form, but over the years it may develop into a persistent or permanent form, however patients with paroxysmal AF (PAF) have a similar risk of IS to those with the persistent or permanent AF. Systematic screening for AF should thus be considered in individuals aged> 75 years or in those at high risk of IS (ref.[1,3,6]).

In patients with AF, oral anticoagulation (OAC) therapy is indicated for the primary and secondary prevention of IS or systemic embolism[1,3,7]. Besides vitamin K antagonists (VKA), direct oral anticoagulants (DOAC) were introduced into clinical practice at the beginning of the last decade. Despite the well-known higher safety and efficacy of DOAC over VKA, even now not all patients with AF have adequate preventive OAC treatment.

The aim of our study was to assess the trends in AF occurrence and the use of OAC in IS patients over the last decade and to evaluate the possible impact of prior use of OAC on admission stroke severity in patients with AF. The results may provide important real-world data about

the prevention of IS in patients with AF. Furthermore, the results may document the trend in AF occurrence in an unselected population of patients, who suffered from IS.

MATERIALS AND METODS

The study population consisted of all consecutive acute IS patients admitted at our stroke center in 2012 and 2021, who were enrolled in the HISTORY (Heart and Ischemic STrOke Relationship studY) prospective observational trial registered on ClinicalTrials.gov (identifier NCT01541163) (ref.[8]). The study protocol was in compliance with the latest Declaration of Helsinki and was approved by the Ethics Committee of our hospital.

All patients underwent computed tomography (CT) or magnetic resonance (MRI) of the brain. In all participants, medical history, baseline demographic and clinical characteristics and vascular risk factors (RVF) were recorded on admission or during the hospitalization. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) on admission. All patients underwent admission ECG, serial laboratory blood samples and ultrasound of cervical and vertebral arteries. In all patients with no history of AF, AF on admission or during the hospital stay at the stroke unit, a 24-hour ECG Holter was performed before discharge. In selected patients with cryptogenic IS, long-term (3–4 weeks) outpatient ECG-Holter monitoring was performed for detection of paroxysmal AF. The type of pharmacological prevention was recorded in all cases, including contraindications for OAC in those with AF. The year-defined group comparison of data and subgroup analysis of patients with known AF were made to assess trends during the studied decade.

Statistical analysis

Statistical software SPSS version 23.0 (Armonk, NY: IBM Corp.) was used for the statistical analysis. Chi-squared and Fisher's exact tests were used to process the qualitative variables. The Mann-Whitney U test was used to compare groups for quantitative variables. Kruskal-Wallis and Mann-Whitney U tests with Bonferroni correction were used to compare NIHSS scores between patients according to treatment with anticoagulants. Data normality was tested using the Shapiro-Wilk test. All tests used an α-level of 0.05 for significance.

RESULTS

In total, 1059 patients (55.9% males, 71.7±12.8 years) with IS were included in the analysis; 459 (55.8% of males, mean age 71.6±12.6 years) patients were enrolled in 2012 and 600 (56.2% males, mean age 71.8±13.1 years) in 2021. Demographic and baseline clinical characteristics are shown in Table 1. Patients admitted in 2012 had coronary heart disease (CHD) more frequently (28.1 vs. 19.7%, P=0.001), arterial hypertension (AH) (86.3 vs. 76.0%, P<0.0001) and less frequently hyperlipidemia (45.8 vs. 52.3%, P=0.034) than those admitted in 2021. No difference was found in regard to AF between 2012

Table 1. Demographic and baseline clinical characteristics of enrolled patients: comparison between the patients enrolled in the years 2012 and 2021.

	2012	2021	*P*
n, males (n, %)	459, 256 (55.8%)	600, 337 (56.2%)	0.898
Age (mean ± SD, years)	71.6 ± 12.6	71.8 ± 13.1	0.640
Admission NIHSS (median)	5.0	5.0	0.908
CHD (n, %)	129 (28.1 %)	118 (19.7%)	0.001
AF presence (n, %)	162 (35.3%)	195 (32.5%)	0.341
Newly diagnosed AF (n, %)	78 (17.0%)	96 (16.0%)	0.665
Known AF (n, %)	84 (18.3%)	99 (16.5%)	0.442
Arterial hypertension (n, %)	396 (86.3%)	456 (76.0%)	<0.0001
Diabetes mellitus (n, %)	142 (30.9%)	192 (32%)	0.712
Hyperlipidemia (n, %)	210 (45.8%)	314 (52.3%)	0.034
Use of statins	157 (34.2%)	207 (34.5%)	0.920
Antiplatelet therapy prior IS (n, %)	171 (37.3%)	160 (26.7%)	0.0002
AC therapy prior IS (n, %)	31 (6.8%)	83 (13.8%)	0.0002
Warfarin (n, %)	24 (5.2%)	36 (6%)	0.591
LMWH (n, %)	4 (0.9%)	4 (0.7%)	0.733
DOAC (n, %)	3 (0.7%)	43 (7.2%)	<0.0001
Dabigatran (n, %)	3 (0.7%)	11 (1.8%)	0.096
Apixaban (n, %)	0	21 (3.5%)	<0.0001
Rivaroxaban (n, %)	0	11 (1.8%)	0.004
Edoxaban (n, %)	0	0	–

AC, anticoagulation; AF, atrial fibrillation; IS, ischemic stroke; CHD, coronary heart disease; OAC, direct oral anticoagulants; LMWH, low molecular weight heparin; SD, standard deviation.

and 2021 (Table 1), but patients admitted in 2021 had used DOAC for AF more frequently before IS (0.7 vs. 7.2%, *P*<0.0001, Table 1).

In patients with known AF before IS, CHD occurred significantly more in the patients admitted in 2012 (54.8 vs. 34.3%, *P*=0.006) (Table 2). Further the number of AF patients on OAC increased substantially (32.1 vs. 70.7%, *P*<0.0001) and the number of AF patients on antiplatelet therapy decreased (42.9 vs. 17.2 %, *P*=0.0001), while the rate of patients with contraindications to OAC did not differ significantly between groups (15.5 vs. 10.1%, *P*=0.274) (Table 2). The number of patients on DOAC increased markedly (3.6 vs. 35.4%, *P*<0.0001), but the rate of patients on VKA did not change (26.2 vs. 31.3%, *P*=0.446, Table 2). No difference was found in the rate of AF patients using warfarin, who had admission INR under lower limit of therapeutic range: 68.2% (15/22) vs. 58.1% (18/31), *P*=0.103).

OAC withdrawal due to surgery (6/86, 7.0%), other severe comorbidities (6/86, 7.0%), previous major bleeding including intracerebral hemorrhage (5/86, 5.8%) and patient's non-compliance to use of OAC (3/86, 3.9%) were the most frequent reasons for absence of OAC treatment or contraindications to OAC in the patients with known AF prior IS (Table 3).

AF patients on OAC had lower admission median NIHSS scores compared to those without OAC in the year 2021 (6 vs. 16, *P*=0.004). A similar trend was also observed in the year 2012, but the difference in the median NHISS score did not reach significance (6 vs. 12, *P*=0.066). No significant difference was found in the rate of patients treated with IV thrombolysis (26.2 vs. 20.2%, *P*=0.408), while the rate of patients treated with endovascular mechanical thrombectomy was higher in the year 2021 (9.5 vs. 25.2%, *P*=0.02). The rate of symptomatic intracerebral hemorrhage did not differ significantly between the groups: 3.3% (1/30) vs. 0% (0/45).

DISCUSSION

In our study, AF patients on OAC before stroke had lower admission median NIHSS scores compared to those without previous OAC treatment (6 vs. 16, *P*=0.004) in the year 2021. Our finding is in line with the recently reported results that anticoagulation before stroke was associated with lower stroke severity in IS patients with known AF (ref.[9]). A tendency of anticoagulation to accelerate a thrombus lysis may contribute to the explanation of this finding[10]. Our finding of low stroke severity in IS patients with AF on OAC also emphasizes the importance of OAC in primary prevention as AF-related stroke has twice the likelihood of being fatal, being more severe and with poorer outcome[2,11]. The difference in the median of admission NIHSS between the patients on OAC and those without OAC treatment was not significant in the year 2012 (6 vs. 12, *P*=0.066). This might be related to the fact that a substantially lower number of patients were on DOACs, which are considered more effective than warfarin.

AF was present in 35.3 reps. 32.5% of IS patients in our study set (Table 1), which was more than estimated or reported previously (20% to 25%) (ref.[2,3,6,12]). Currently, the rates of AF in IS patients are being considered underestimated and in a case of use of a combination of

Table 2. Subgroup comparison of the patients with known atrial fibrillation before ischemic stroke.

	2012	2021	*P*
n	84	99	
Males (n, %)	42 (50%)	42 (42.4%)	0.305
Age (mean ± SD, years)	78.1 ± 8.6	79.5 ± 9.3	0.196
Admission NIHSS (median)	9.0	8.0	0.763
CHD (n, %)	46 (54.8%)	34 (34.3%)	0.006
Arterial hypertension (n, %)	78 (92.9%)	84 (84.9%)	0.090
Diabetes mellitus (n, %)	30 (35.7%)	38 (38.4%)	0.710
Hyperlipidemia (n, %)	35 (41.7%)	46 (46.5%)	0.515
Use of statins (n, %)	34 (40.5%)	42 (42.7%)	0.790
No prior AC therapy for AF	57 (67.9%)	29 (29.3%)	<0.0001
Antiplatelet therapy (n, %)	36 (42.9%)	17 (17.2%)	0.0001
AC therapy prior IS (n, %)	27 (32.1%)	70 (70.7%)	<0.0001
Warfarin (n, %)	22 (26.2%)	31 (31.3%)	0.446
LMWH (n, %)	2 (2.4%)	4 (4%)	0.689
DOAC (n, %)	3 (3.6%)	35 (35.4%)	<0.0001
Dabigatran	3 (3.6%)	9 (9.1%)	0.133
Apixaban	0	17 (17.2%)	<0.0001
Rivaroxaban	0	9 (9.1%)	0.004
Edoxaban	0	0	NA
Contraindications to the AC therapy (n, %)	13 (15.5%)	10 (10.1%)	0.274

AC, anticoagulation; AF, atrial fibrillation; CHD, coronary heart disease; DOAC, direct oral anticoagulants; IS, ischemic stroke; LMWH, low molecular weight heparin; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

Table 3. Most frequent reasons for absence of OAC treatment and most frequent contraindications to OAC treatment in the patients with known atrial fibrillation before ischemic stroke.

	2012	2021	*P*
Number of patients without OAC (n, %)	57 (67.9%)	29 (29.3%)	<0.0001
Non-compliance to OAC (n, %)	3 (5.2%)	0	0.305
Prior ICH (n, %)	2 (3.5%)	0	0.763
Prior major bleeding excl. ICH (n, %)	1 (1.7%)	2 (6.9%)	0.109
Withdrawal due to surgery (n, %)	0	6 (20.7%)	0.001
Cancer (n, %)	1 (1.7%)	0	0.906
Severe hepatopathy (n, %)	0	1 (3.4%)	0.603
Other severe comorbidities (n, %)	5 (8.8%)	1 (3.4%)	0.317

ICH, intracerebral hemorrhage; OAC, oral anticoagulants.

Fig. 1. The proportions of patients with AF in 2012 and 2021.

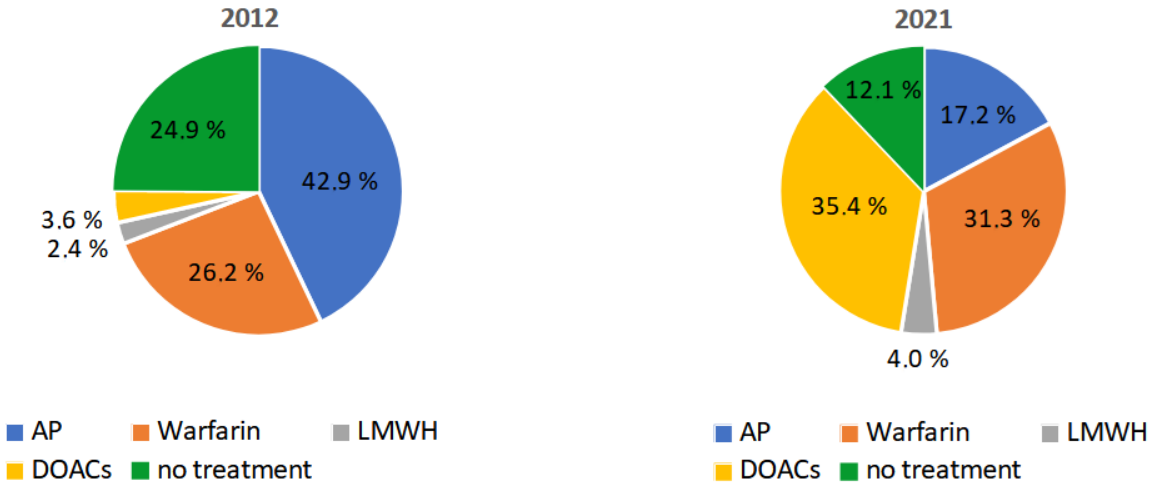

Fig. 2. The proportions of individual types of antithrombotic treatment in patients with AF in 2012 and 2021.
AP, antiplatelet therapy; DOACs, direct oral anticoagulants; LWMH, low molecular weighted heparin.

different screening methods for the detection of AF in IS patients, the rate of detected AF ranges between 20–25%, and could be even higher if screening is focused strictly on patients with cryptogenic IS and ESUS (Embolic Stroke of Undetermined Source) stroke[2,13]. Current guidelines also recommend considering prolonged ECG monitoring including long-term Holter ECG monitoring or implantable loop recorder (ILR) in the selected IS patients with risk of AF (ref.[1,3,6]). In half of our IS patients with AF, the arrhythmia was detected as a new one during the hospitalization or after the discharge using outpatient long-term ECG Holter monitoring (Table 1).

In our study, no difference was observed in the rates of IS patients with known AF between the years 2012 and 2021 (Table 1), however more patients were on OAC and also on DOAC in the year 2021 (Table 1) and thus, a lower rate of IS patients with known AF would be expected in that year. We may speculate that not all patients

on DOAC had optimal therapeutic dose of DOAC or they did not use DOAC regularly, as well as not all patients on warfarin had optimal value of INR. Current emerging evidence suggests that patients with known AF before IS have a higher risk of stroke recurrence than patients with AF detected after IS (ref.[14]). Furthermore, the risk of recurrent stroke is higher in the those with a pre-existing anticoagulation than those who were naive to anticoagulation before IS (ref.[15-17]).

No difference was found in the rates of patients with newly detected AF after IS between compared years in our study (Table 1, Fig. 1). This finding may correspond to the fact that most patients with cryptogenic IS underwent the same diagnostic protocol for the detection of AF after IS.

We found that more patients used OAC for AF in the year 2021, despite a similar rate of contraindications to OAC treatment (Table 2), while the number of patients on antiplatelet therapy decreased (Table 2). These findings indicate a trend of better pharmacological prevention in AF patients, however, one third of patients with AF did not used OAC in our study, which was similar to the rates from previous reports[9,18]. The observed increased rate of patients on OAC was caused mainly by a higher rate of patients on DOAC, while the rates of patients on warfarin did not differ between compared years (Table 2, Fig. 2). The observed higher rate of patients on DOAC in the year 2021 was associated with several factors: a) the start of covering the cost of DOAC by health insurance companies after their introduction on the market after year 2012, b) increased awareness among cardiologists about DOAC. Nevertheless, geographical variations were found in the prescription of DOAC over VKA in Europe, the Northern and Western European countries being those, where DOAC were most prescribed[12,19]. In our study, the rate of patients using VKA did not differ between compared years (Table 2, Fig. 2) and substantial number of patients had the admission INR under the lower limit of therapeutic range. We may suggest two main reasons for the unchanged rate of patients on warfarin during the last decade: substantially lower prize of VKA in comparison to DOACs and strict prescription limit of DOACs for practitioners in primary prevention.

In our study, patients admitted for IS in the year 2021 had less frequently AH, and CHD (Table 1). These differences may be related to an improvement of the prevention of cardiovascular diseases[20]. On contrary, hyperlipidemia was more frequent in the year 2021 (Table 1). This finding may be related to fact that laboratory criteria for diagnosis of hyperlipidemia were changed toward lower values of lipid molecules, especially LDL-cholesterol. Furthermore, hyperlipidemia was probabily more often diagnosed also due to better primary prevention. The age of our patients with AF was similar to previous reports and our patients also did not substantially differ from the previous studies in the sex distribution[2,12,21,22]. Our patients also did not differ from previous reports in the rates of concomitant diseases except the presence of diabetes mellitus, which was more frequent in comparison to recent reports (35.7 resp. 38.4% vs. 22.5–29.5%) (ref.[17]). This finding might be related to a generally high prevalence of diabetes in our population.

Our study has several limitations. Firstly, a retrospective design of the study analysis, however, the data of all patients included in this study analysis were collected prospectively following the protocol of the HISTORY study. A single-center experience may limit a common translation of the observed results to a general population. Not all enrolled IS patients underwent or completed an extended diagnostic protocol for the detection of AF including the long-term ECG Holter, thus the occurrence of AF might exceed the reported rate.

CONCLUSION

In conclusion, AF patients on OAC had lower admission median of NIHSS score compared to those without previous OAC treatment and AF patients were mostly treated with DOAC in the year 2021. The AF was present in 35.3 (2012) and 32.5% (2021) of our IS patients. The number of AF patients using warfarin did not change during the last decade and substantial number of these patients had the admission INR under lower limit of therapeutic range in both compared years. Our results provide important real-world data, which may document reliably the current trends in the prevention of IS in patients with AF and might contribute to the further improvement of IS prevention.

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