

# Anticoagulant therapy in secondary stroke prevention in patients with atrial fibrillation

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## ABSTRACT:

**Background:** Atrial fibrillation (AF) is one of the most important risk factors for ischemic stroke. It is not completely known whether ischemic stroke patients with AF that use oral anticoagulant therapy are at increased risk for further recurrent strokes or how ongoing secondary prevention should be managed. The aim of this study is to determine the role of anticoagulant therapy in secondary stroke prevention in patients with AF.

**Materials and Methods:** A retrospective analysis was made of 98 patients with acute stroke and AF hospitalized at the University Clinic for Neurology in Skopje, N. Macedonia at the Department of Urgent Neurology in the period from 2019 to 2022. Inclusion criteria for the study were patients with AF, in all age groups, diagnosed with stroke. In the analysis, we also included other parameters such as neurological deficit quantified by NIHSS (National Institutes of Health Stroke Scale), state of consciousness quantified by GCS (Glasgow Coma Scale/Score) and degree of disability quantified by mRS (Modified Rankin Scale).

**Results:** The results of this study showed that group 1A (known AF) patients had a predominance of moderate to severe stroke (quantified by NIHSS score), moderate disability (quantified by mRS score), low GCS score, compared to group 1B (newly diagnosed AF) patients with a predominance of mild stroke, mild disability, but without proven statistical significance ( $p > 0.05$ ). It was also found that even though the patients were treated with anticoagulant therapy, they still had developed a stroke.

**Conclusion** In this study, it was concluded that patients, despite receiving anticoagulant therapy, still had developed a stroke. It might be related with incompliance, reduced pharmacological efficacy of the anticoagulant in individual patients, or other factors such as alternative stroke mechanisms (eg, small vessel occlusion). Regular monitoring and good patient education are important for successful treatment.

**KEYWORDS:** atrial fibrillation, stroke, anticoagulant therapy, secondary prevention

## SAŽETAK:

ANTIKOAGULANTNA TERAPIJA U SEKUNDARNOJ PREVENCIJI MOŽDANOG UDARA U BOLESNIKA S FIBRILACIJOM ATRIJA

**Uvod:** Fibrilacija atrijska (FA) jedan je od najvažnijih čimbenika rizika za ishemijski moždani udar. Nije u potpunosti poznato jesu li bolesnici koji su preboljeli moždani udar i imaju FA radi koje uzimaju oralnu antikoagulantnu terapiju pod većim rizikom ponovnih moždanih udara ili kako bi se trebalo

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postupati s postojećom sekundarnom prevencijom. Cilj ovog istraživanja je odrediti ulogu antikoagulantne terapije u sekundarnoj prevenciji moždanog udara u bolesnika s FA.

**Materijali i metode:** Provedena je retrospektivna analiza 98 bolesnika s moždanim udarom i FA hospitaliziranih na Sveučilišnoj klinici za neurologiju u Skopju, Sj. Makedonija, na Odjelu za hitnu neurologiju u periodu od 2019. do 2022. Godine. U analizu su uključeni i drugi pokazatelji poput neurološkog deficita kvantificiranog NIHSS skalom (engl. National Institutes of Health Stroke Scale), stanje svijesti procijenjeno GCS zbrojem (engl. Glasgow Coma Scale/Score) i stupanj neurološkog deficita kvantificiranog pomoću mRS (engl. Modified Rankin Scale).

**Rezultati:** Rezultati su pokazali da je su bolesnici u grupi 1A (poznata FA) imali češći srednje težak do težak moždani udar (kvantificiran NIHSS zbrojem), srednje težak neurološki deficit (kvantificiran mRS zbrojem), niži GCS zbroj, naspram bolesnika u skupini 1B (novootkrivena FA) koji su češće imali blaži moždani udar, blaži neurološki deficit, ali bez statističkog značaja ( $p > 0.05$ ). Iako su bolesnici bili na antikoagulantnoj terapiji, svejedno su razvili moždani udar.

**Zaključak:** Prema našim rezultatima, unatoč antikoagulantnoj terapiji bolesnici su razvili moždani udar. Ovo može biti povezano s nekomplijentnosti, smanjenom farmakološkom učinkovitosti antikoagulantnih lijekova u pojedinim bolesnika ili drugih čimbenicima poput alternativnih mehanizama za razvoj moždanog udara (npr. okluzija malih krvnih žila). Redovito praćenje i dobra edukacija bolesnika su važni za uspješno liječenje.

**KLJUČNE RIJEČI:** fibrilacija atriya, moždani udar, antikoagulantna terapija, sekundarna prevencija

## INTRODUCTION

Atrial fibrillation (AF) is one of the most important risk factors for ischemic stroke. It is known that patients with AF have a 5 times higher risk of having a stroke than those without AF. With the availability of modern cardiac monitoring technologies, detection of AF after stroke or transient ischemic attack (TIA) has improved significantly [1].

Although the burden of AF-related stroke is high, AF is a potentially treatable risk factor. Numerous studies have revealed that vitamin K antagonists, such as warfarin, or non-vitamin K antagonist oral anticoagulants (NOACs), such as rivaroxaban, dabigatran, and edoxaban, reduce the risk of ischemic stroke. Based on these data, current guidelines recommend warfarin or NOACs over aspirin for stroke prevention in the high-risk patients with AF [2].

It is not known whether patients with ischemic stroke and AF, despite oral anticoagulant therapy, are at increased risk for further recurrent strokes or how ongoing secondary prevention should be managed [3].

AF causes one-fifth of ischemic strokes, with a high risk of early recurrence. Although long-term anticoagulation is highly effective for stroke prevention in AF, initiation after stroke is usually delayed by concerns over intracranial hemorrhage risk. NOACs offer a significantly lower risk of intracranial hemorrhage than other anticoagulants, potentially allowing earlier anticoagulation and prevention of recurrence, but the safety and efficacy of this approach has not been established [4].

Despite strong evidence of efficacy, OAC use is limited by nonprescription ( $\approx 50\%$  patients do not receive OAC, despite an appropriate indication), nonadherence (30% 1-year discontinuation for warfarin), and subtherapeutic dosing ( $\approx 25\%$ – $38\%$  of warfarin-treated patients) [5].

## AIM

The aim of this study is to determine the role of anticoagulant therapy in secondary stroke prevention in patients with AF.

## MATERIALS AND METHODS

A retrospective analysis was made of 98 acute stroke patients with AF hospitalized at the University Clinic of Neurology in Skopje, N. Macedonia, at the Department of Urgent Neurology in the period from 2019 to 2022.

Inclusion criteria for the study were patients with AF, in all age groups, diagnosed with stroke (ischemic, hemorrhagic). Depending on whether it is known AF or newly diagnosed AF, we divided the patients into two groups: 1A known atrial fibrillation and 1B newly diagnosed atrial fibrillation (AF de novo).

According to the localization of the stroke registered on computed tomography (CT) of the brain, we divided the patients into two groups: 2A patients with a stroke in the anterior circulation, 2B patients with a stroke in the posterior circulation.

In the analysis, we also included other parameters such as neurological deficit quantified by NIHSS (National Institutes of

Health Stroke Scale), state of consciousness quantified by GCS (Glasgow Coma Scale/Score) and degree of disability quantified by mRS (Modified Rankin Scale). Depending on the NIHSS score, we divided stroke patients into 3 categories: mild stroke (1-5 points), moderate stroke (5-14 points), severe stroke (15-42 points). Depending on the GCS result, we divided the patients according to the level of consciousness into 3 groups: best response (15-9 points), coma (8-4 points), completely unresponsive (< 3 points). Depending on the mRS score, we divided the patients according to the degree of disability into: patients with mild disability (1-2 points), patients with moderate disability (3-4 points), patients with severe disability (5 points).

### STATISTICAL ANALYSIS

The data were analyzed using IBM SPSS Statistics (chi square test) and the (chi-square) test was used, which is expressed in numbers and percentages. The results are presented tabular and graphically. Statistical significance was set at  $p < 0.05$ .

### RESULTS

In our study, 98 patients aged 49-89 years were analyzed, of which 53.1% (52) were women and 46.9% (46) were men. 72.5% (71) of the patients had an ischemic stroke, 7.1% (7) had a hemorrhagic stroke, and 20.4% (20) had an ischemic stroke with hemorrhagic transformation. (figure 1).

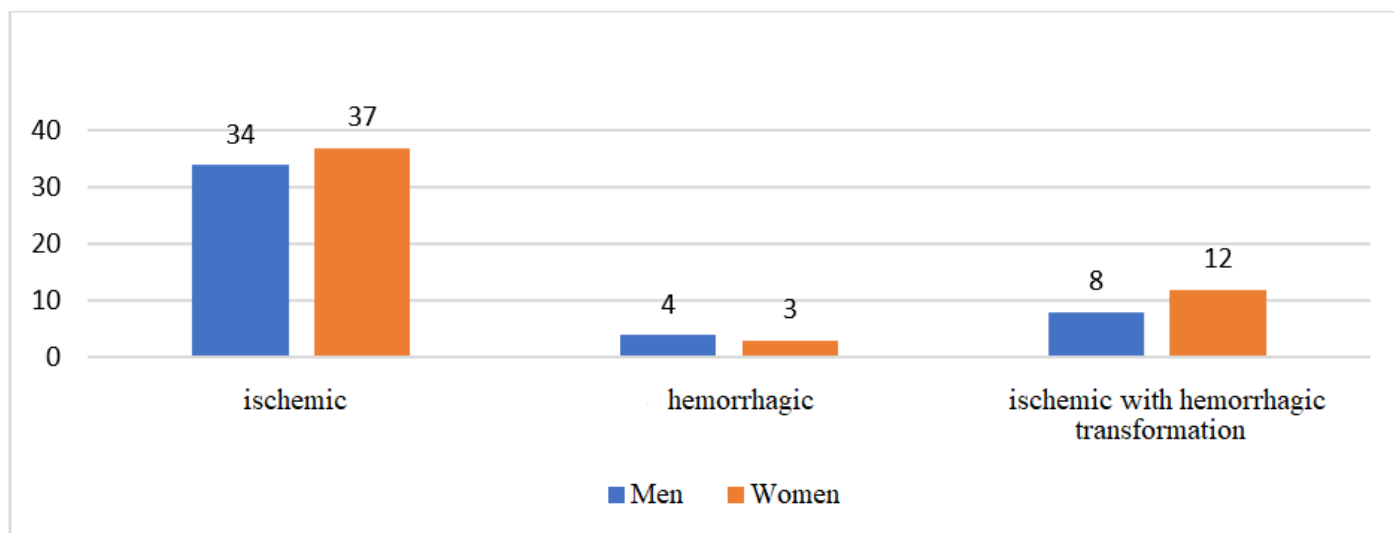


Figure 1. Distribution of the total number of patients according to gender and type of stroke

According to the localization of the stroke, 78.6% (77) of the patients had a stroke localized in the anterior circulation, and 19.4% (19) had a stroke localized in the posterior circulation. (table 1)

Table 1. Localization of the stroke and the number of patients

Localization of stroke Gender	1 –Anterior circulation		2 –Posterior circulation		3 - Thrombolysed		In total No.	In total %
	No.	%	No.	%	No.	%		
1 -Male	36	36,7%	8	8,2%	2	2,0%	46	46,9%
2 -Female	41	41,8%	11	11,2%		0,0%	52	53,1%
<b>Total sum</b>	<b>77</b>	<b>78,6%</b>	<b>19</b>	<b>19,4%</b>	<b>2</b>	<b>2,0%</b>	<b>98</b>	<b>100,0%</b>

Out of a total of 98 patients, 63.3% (62) had known AF (group 1A), of which 26.5% (26) were men, and 36.7% (36) were women. In 36.7% (36) of the patients, AF was newly diagnosed during hospitalization (group 1B), of which 20.4% (20) were men, and 16.3% (16) were women (Figure 2).

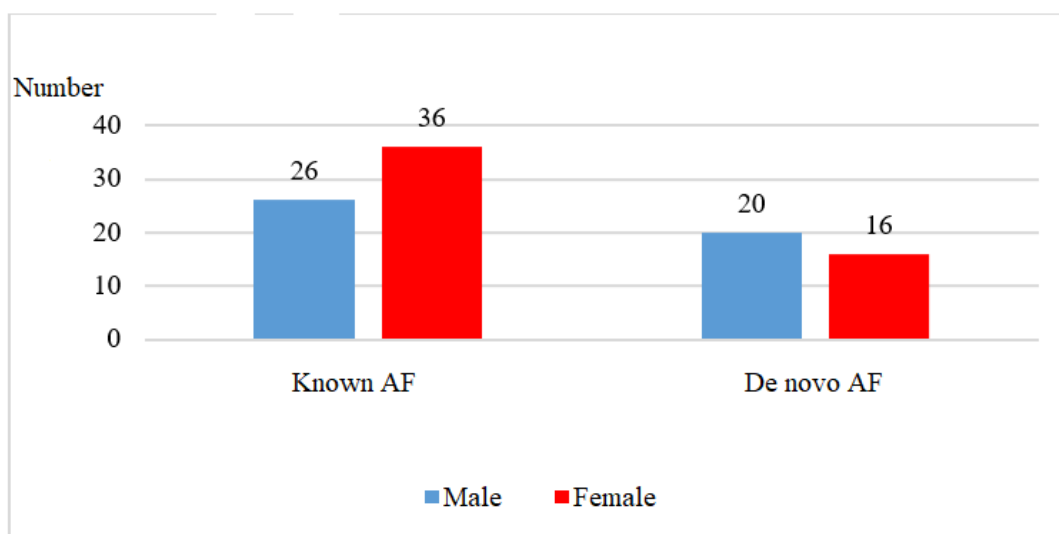


Figure 2. Patients with known versus newly diagnosed AF

$X^2=1,696 < X^2(1 \text{ and } 0,005)=3,841$  and  $p>0,05$

$H_0$  (null hypothesis) is accepted. There is no association between AF and gender.

According to the score obtained from NIHSS; 25% of subjects from group 1A (known AF) had a mild stroke, 65% had a moderate stroke, 64.8% had a severe stroke. 75% of the individuals from group 1B (AF de novo) had a mild stroke, 35% a moderate stroke and 35.2% a severe stroke. (table 2, figure 3).

Table 2. NIHSS score (at discharge) of patients with known versus newly diagnosed AF.

Known AF	Count	1	26	35	62
	% within NIHSS	25,0%	65,0%	64,8%	63,3%
De novo AF	Count	3	14	19	36
	% within NIHSS	75,0%	35,0%	35,2%	36,7%
Total	Count	4	40	54	98
	% within NIHSS	100,0%	100,0%	100,0%	100,0%

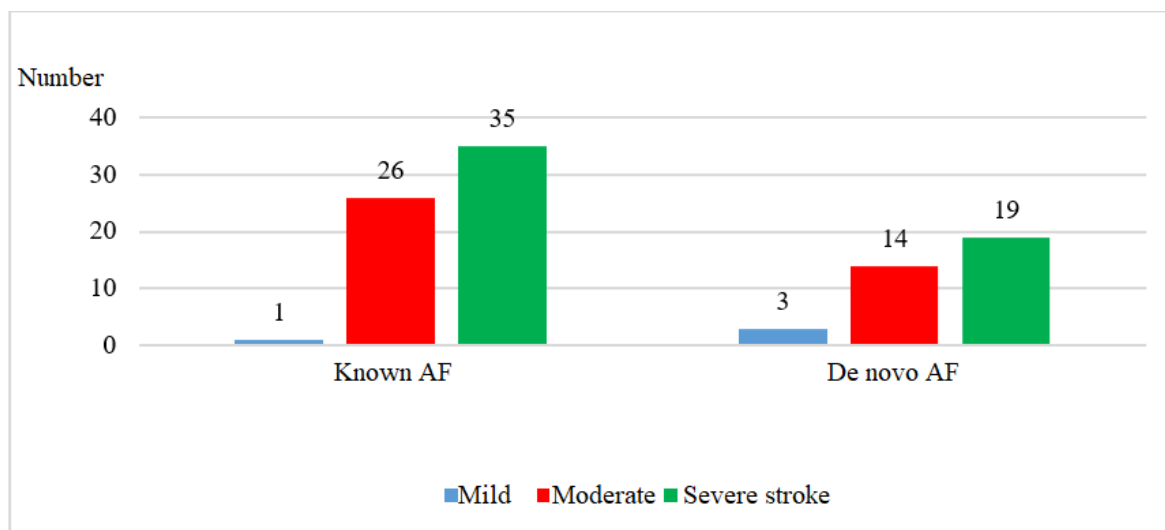


Figure 3. NIHSS score (at discharge) of patients with known versus newly diagnosed AF

$X^2=2,628 < X^2(2 \text{ and } 0,05)= 5,991$  and  $p>0,05$

H0 (null hypothesis) is accepted. There is no association between AF and NIHSS.

According to the result obtained by GCS, 62% of subjects from group 1A (known AF) had the best response, 70.8% were in coma, 33.3% were completely unresponsive. 38.0% of the patients from group 1B (AF de novo) had the best response, 29.2% were in a coma, 66.7% were completely unresponsive. (Table 3, Figure 4).

Table 3. GCS result (at discharge) of patients with known versus newly diagnosed AF

		Best response	Coma	Completely unresponsive	Total	
AF	Known AF	Count	44	17	1	62
		% within GCS	62,0%	70,8%	33,3%	63,3%
AF	De novo	Count	27	7	2	36
		% within GCS	38,0%	29,2%	66,7%	36,7%
Total		Count	71	24	3	98
		% within GCS	100,0%	100,0%	100,0%	100,0%

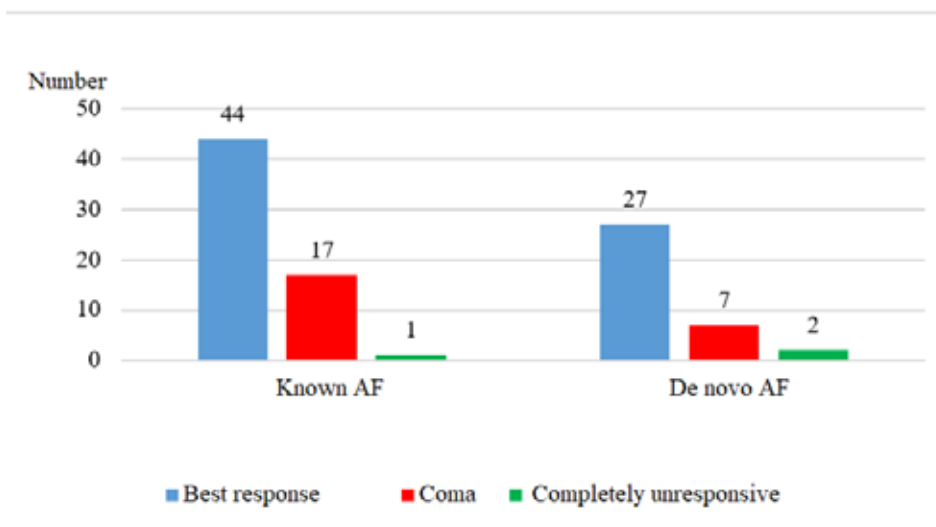


Figure 4. GCS result (at discharge) of patients with known versus newly diagnosed AF

$X^2=1,799 < X^2(2 \text{ and } 0,05)= 5,991$  and  $p>0,05$

H0 (null hypothesis) is accepted. There is no association between AF and GCS.

According to the result obtained from the mRS, 50.0% of the respondents from group 1A (known AF) had light disability, 66.7% moderate disability, 62.9% severe disability. 50.0% of the respondents from group 1B (AF de novo) had mild disability, 33.3% moderate disability, 37.1% severe disability. (Table 4, Figure 5).

Table 4. mRS result (at discharge) of patients with known versus newly diagnosed AF

		Light disability	Moderate disability	Severe disability	Total
Known AF	Count	2	16	44	62
	% within mRS	50,0%	66,7%	62,9%	63,3%
De novo AF	Count	2	8	26	36
	% within mRS	50,0%	33,3%	37,1%	36,7%
Total	Count	4	24	70	98
	% within mRS	100,0%	100,0%	100,0%	100,0%

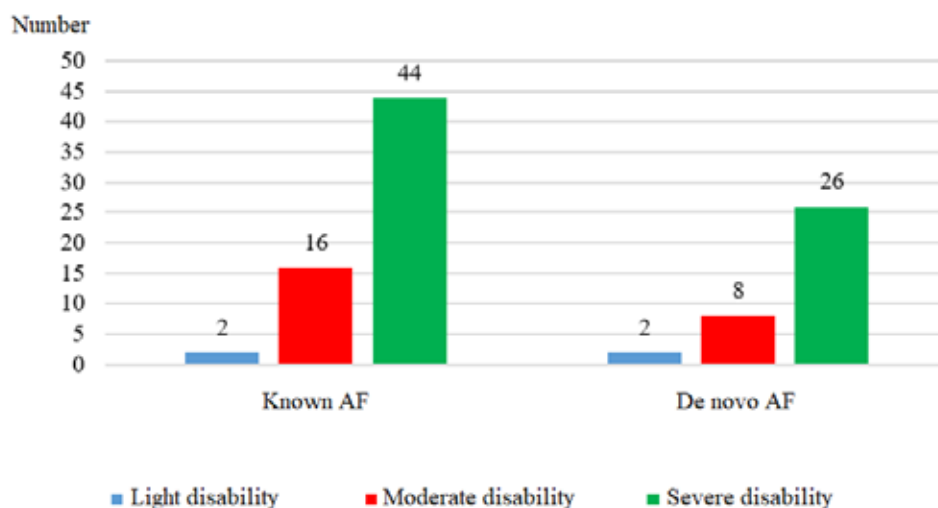


Figure 5. mRS result (at discharge) of patients with known versus newly diagnosed AF

$X^2=0,427 < X^2 (2 \text{ and } 0,05)= 5,991$  and  $p>0,05$   
 H0 (null hypothesis) is accepted. There is no association between AF and mRS.

According to therapy before admission, 45.5% of group 1A (Known AF) and 54.5% of group 1B (AF de novo) received antiaggregation therapy. Anticoagulant therapy received 97.5 % of patients with known AF and 2.5% of patients with AF de novo. Patients who did not receive therapy were 36.1% in group 1A and 63.9% in group 1B.

Table 5. Therapy before hospital admission

		Antiaggregation therapy	Anticoagulant therapy	No therapy
Known AF	Count	10	39	13
	% within therapy before admission	45,5%	97,5%	36,1%
De novo AF	Count	12	1	23
	% within therapy before admission	54,5%	2,5%	63,9%
Total	Count	22	40	36
	% within therapy before admission	100,0%	100,0%	100,0%

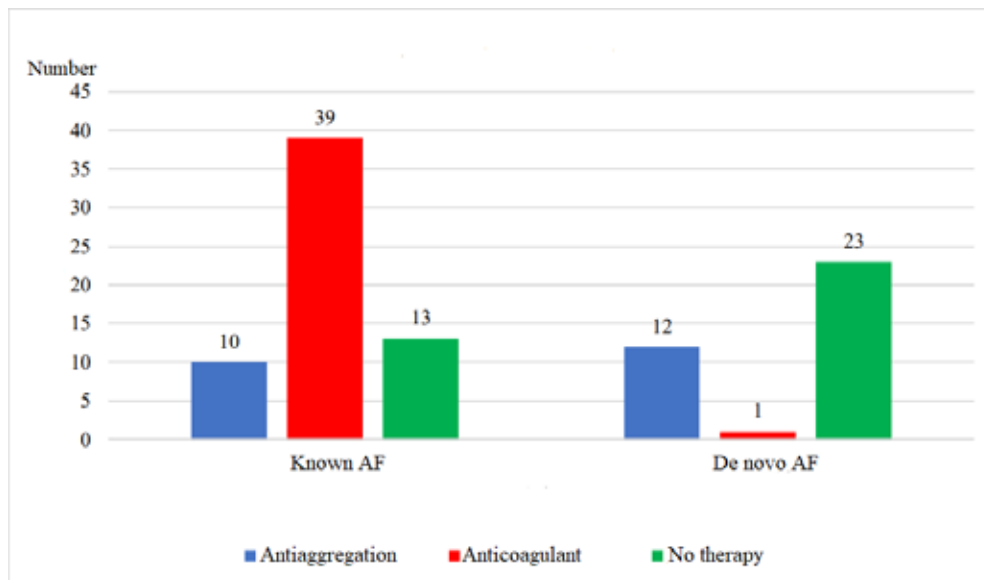


Figure 6. Therapy before hospital admission

$X^2=34,597 < X^2(2 \text{ and } 0,005) = 5,991$  and  $p < 0,05$

H0 (null hypothesis) is rejected and H1 (working or alternative hypothesis) is accepted.

There is association between AF and pre-admission therapy.

## DISCUSSION

In our study, in the period from 2019 to 2022, 98 patients with AF were hospitalized and treated at the Department of Urgent Neurology, due to a registered acute stroke. This study includes patients with AF. Other risk factors for acute stroke, such as diabetes mellitus, hypertension, hyperlipidemia, were not analyzed in the study. Also, the results obtained with NIHSS, GCS and mRS were obtained when the patients were discharged from the hospital. The results showed that 36.7% (36) of the subjects were diagnosed with AF for the first time. The largest number of patients had ischemic stroke (72.5%), but the rate of patients with ischemic stroke with hemorrhagic transformation (20.4%) is also significant. In our group of patients dominates a stroke in anterior circulation (78.6%).

The results of this study showed that group 1A (known AF) patients had a predominance of moderate to severe stroke (quantified by NIHSS score), moderate disability (quantified by mRS score), low GCS score, compared to group 1B (AF de novo) patients with a predominance of mild stroke, mild disability, but without proven statistical significance ( $p > 0.05$ ).

Also it was concluded that patients, despite receiving anticoagulant therapy, still had a stroke. It might be related with noncompliance, reduced pharmacological efficacy of the anticoagulant in individual patients, or other factors such as alternative stroke mechanisms (eg, small vessel occlusion).

One of the first studies to ask the question, “Why do strokes occur in patients with atrial fibrillation who receive anticoagulant therapy?” is the study by David J Seiffge et al.

The study suggested that one possible reason is the failure to follow the prescribed anticoagulation therapy before the initial event. A significant majority (73%) of patients using VKA medication before the initial event had INR levels below the therapeutic range, which suggests poor adherence to the treatment regimen. Among those patients who continued using VKA after the event, 61% experienced further recurrent ischemic strokes with subtherapeutic INR values, indicating that poor adherence might have played a role, despite their prior experience of a significant outcome event, i.e., ischemic stroke. However, it's important to note that patients who initiate NOACs for secondary prevention typically demonstrate high adherence rates, making this less likely to be a complete explanation. Additionally, patients who had not previously used oral anticoagulants (OAC) before experiencing a stroke were found to have lower adherence rates compared to those with prior anticoagulant use, which contradicts the direction of bias suggested by our findings. Furthermore, a recent analysis in a study conducted in Japan revealed that in patients taking VKA, having an INR of  $\geq 2.0$  at the onset of a stroke was linked to a higher risk of recurrent ischemic stroke [3].

The study also says that genetic variability could be a cause of susceptibility to recurrent stroke in patients with AF. “Two genes (CYP2C9 and VKORC1) may play a role in individual patient response to and efficacy of VKA, but no such variability of response is known for NOACs. However, most patients who changed anticoagulation after the event were switched from VKA



to a NOAC (76%), so a genetic variability in 1 of the aforementioned genes is not likely to explain the high continued ischemic stroke risk we observed”[3].

A study from Oldgren et al. concluded that early initiation was noninferior to delayed start of NOAC after acute ischemic stroke in patients with AF [6]. Numerically lower rates of ischemic stroke and death and the absence of symptomatic intracerebral hemorrhages implied that the early start of NOAC was safe and should be considered for acute secondary stroke prevention in patients eligible for NOAC treatment.

The study is known as TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation - registry-based, randomized, noninferiority, open-label, blinded end-point study at 34 stroke units using the Swedish Stroke Register for enrollment and follow-up). Within 72 hours from stroke onset, patients were randomized to early ( $\leq 4$  days) or delayed (5-10 days) NOAC initiation, with choice of NOAC at the investigators' discretion. The primary outcome was the composite of recurrent ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality at 90 days. The prespecified noninferiority margin was 3%. Secondary outcomes included the individual components of the primary outcome [6].

Other study (Optimal timing of anticoagulation after acute ischemic stroke with atrial fibrillation (OPTIMAS)) investigated whether early treatment with a direct oral anticoagulant, within four days of stroke onset, is as effective or better than delayed initiation, 7 to 14 days from onset, in atrial fibrillation patients with acute ischemic stroke. The primary outcome is a composite of recurrent stroke (ischemic stroke or symptomatic intracranial hemorrhage) and systemic arterial embolism within 90 days. Secondary outcomes include major bleeding, functional status, anticoagulant adherence, quality of life, health and social care resource use, and length of hospital stay [4].

Data from Paciaroni et al. showed that the best time for initiating anticoagulation treatment for secondary stroke prevention is 4 to 14 days from stroke onset. Moreover, patients treated with oral anticoagulants alone had better outcomes compared with patients treated with low molecular weight heparins alone or before oral anticoagulants [7].

A study from Klijn et al. suggests that assessing the size and severity of the index infarct or stroke is crucial before deciding on measures to reduce the risk of hemorrhagic transformation of the infarct or other intracranial bleeding[8]. While studies have linked hemorrhagic transformation and infarct size to poorer outcomes [7], there is a lack of randomized data to confirm that early anticoagulation poses greater risks, potentially leading to more harm in patients with larger infarcts. Nevertheless, in the absence of definitive data, many expert clinicians currently recommend taking into account stroke severity and infarct size when determining the optimal timing for anticoagulation [8]. For patients with mild strokes and small infarcts ( $<1.5$  cm), some experts suggest that anticoagulation treatment may be suitable

around the third or fourth day following the initial stroke.

In cases of moderate infarcts, it is recommended to initiate anticoagulation treatment around the seventh day from the initial stroke.

In situations involving large infarcts, it may be advisable to delay anticoagulation treatment for up to 14 days after the initial stroke [8].

According to the European Heart Rhythm Association guidelines, for patients with TIA and AF, VKAs or NOACs can be started as early as the first day. For those already on VKAs or NOACs, treatment can continue due to a low risk of intracranial hemorrhage (ICH). For patients with mild strokes (NIHSS $<8$ ), NOACs can be initiated within three days or after ruling out ICH through imaging (computed tomography or magnetic resonance imaging). For moderate strokes (NIHSS 8–16), anticoagulation can commence at 5–7 days, and for severe strokes (NIHSS  $>16$ ), it may be delayed until 12–14 days.

Recently published ELAN study was an open-label trial at 103 sites in 15 countries to analyze the effect of early vs later initiation of NOACs in persons with AF who have had an acute ischemic stroke [9]. They included 2013 participants (37% with minor stroke, 40% with moderate stroke, and 23% with major stroke). Of them, 1006 were assigned to early anticoagulation (within 48 hours after a minor or moderate stroke or on day 6 or 7 after a major stroke) and 1007 on later anticoagulation (day 3 or 4 after a minor stroke, day 6 or 7 after a moderate stroke, or day 12, 13, or 14 after a major stroke). The primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days after randomization. Secondary outcomes included the components of the composite primary outcome at 30 and 90 days. By 30 days, a primary-outcome event occurred in 29 participants (2.9%) in the early-treatment group and 41 participants (4.1%) in the later-treatment group. Recurrent ischemic stroke occurred in 14 participants (1.4%) in the early-treatment group and 25 participants (2.5%) in the later-treatment group by 30 days and in 18 participants (1.9%) and 30 participants (3.1%), respectively, by 90 days. Symptomatic intracranial hemorrhage occurred in 2 participants (0.2%) in both groups by 30 days. Authors concluded that the incidence of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death at 30 days ranged from 2.8 percentage points lower to 0.5 percentage points higher (based on the 95% confidence interval) with early than with later use of DOACs.

Two large randomized intervention studies (IST and CAST) have shown that administering aspirin within 48 hours of a stroke only marginally reduces case fatality and the recurrence of strokes [10,11]. A meta-analysis revealed a slight reduction in the combined outcome of death or non-fatal recurrent stroke (nine per 1000 patients treated). This benefit was observed even in patients with AF. Therefore, it's reasonable to administer aspirin

(100–300 mg/day) within 48 hours after an acute ischemic stroke or TIA for short-term treatment, while awaiting the introduction of anticoagulation [10,11].

Randomized Controlled Trials (RCTs) have failed to provide evidence supporting the use of anticoagulants in patients with acute ischemic stroke within the first 48 hours of stroke onset. Therefore, in patients already taking VKAs, it may be considered to temporarily discontinue anticoagulant therapy, conduct a follow-up brain CT scan within 24–72 hours, and decide when to restart treatment based on the size of the lesion. Consequently, until more evidence becomes available, aspirin should be administered to all patients during this acute time frame [8].

They consider it reasonable to start anticoagulant therapy at day 3 or 4 from the index stroke in patients with mild stroke and small infarcts (<1.5 cm) and at day 7 for moderate infarcts. [8] For large infarcts, anticoagulation treatment might be best delayed for 14 days after the index stroke. [3]

The risk of early recurrent ischemic stroke occurring within the first 2 weeks, is higher in patients with AF than in patients with stroke resulting from other causes. In patients with AF and acute ischemic stroke, unfractionated heparin (UFH), LMWH, or heparinoids are commonly used in routine clinical practice outside clinical trials while awaiting the commencement or effect of OAC. However, RCTs indicate that in patients with acute cardioembolic stroke, early anticoagulation with UFH or LMWH is associated with increased intracranial bleeding, a non-significant reduction in recurrence of ischemic stroke, and no substantial reduction in death and disability. Furthermore, observational studies reported that patients who had received VKA alone had a significantly lower risk of bleeding events, compared with patients treated with LMWH followed by OAC [8].

According to Ahmad and Lip's study, bleeding is the most feared complication of antithrombotic therapy, and this can limit the prescription of oral anticoagulants. The HAS-BLED score is a simple tool to aid clinicians in undertaking a bleeding risk assessment and prompts them to consider the correctable risk factors for bleeding, such as labile international normalized ratios (INRs), uncontrolled hypertension and concomitant drugs. It can periodically be reassessed and has been validated in various large real-world cohorts, performing favourably compared with other bleeding risk scores. The HAS-BLED score has been incorporated into international guidelines [12].

According to one study, adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have atrial fibrillation. Warfarin is substantially more efficacious (by approximately 40%) than antiplatelet therapy. Absolute increases in major extracranial hemorrhage associated with antithrombotic therapy in participants from the trials included in this meta-analysis were less than the absolute reductions in stroke. Judicious use of antithrombotic therapy importantly reduces stroke for most patients who have atrial fibrillation [13].

Although warfarin has been a highly effective treatment to reduce stroke in AF, its limitations are well known by physicians and patients. New oral anticoagulants have been shown to be convenient and to have important advantages in improving clinical outcomes, including fewer strokes, less intracranial hemorrhage, and lower mortality. These benefits are consistent whether or not patients have been on warfarin previously. Moreover, the cost appears to be acceptable, particularly in light of the major advantage with regard to convenience. Thus, the newer agents should generally be used as first-line treatment for stroke prevention in AF.

Some have suggested that although the new agents provide important benefits for patients not previously on warfarin, there is little advantage to switching if patients are tolerating warfarin with good INR control. Although on the surface this conclusion seems rational, it is not supported by the data. The benefits of the new anticoagulants were similar regardless of prior use of warfarin [14]. With dabigatran, there was no statistically significant evidence of less benefit of stroke prevention in centers with better INR control. Importantly, the benefit of dabigatran over warfarin in reducing intracranial hemorrhage appeared to be nearly identical across INR control ranges. The pattern of a consistent benefit regardless of INR control appears to be the case for rivaroxaban and apixaban as well [15].

Among new-onset AF patients, non-vitamin K antagonist oral anticoagulant use has increased and antiplatelet monotherapy has decreased. However, anticoagulation is used frequently in low-risk patients and inconsistently in those at high risk of stroke. Significant geographic variability in anticoagulation persists and represents an opportunity for improvement [16].

We should acknowledge the various limitations of this study. First, this was a retrospective observational analysis. Unlike randomized studies, the selection of patients and undocumented confounding factors could affect the validity of our findings. However, it was impossible to randomize patients with stroke and AF. Secondly, there were not studies that examine the GCS score on patients with known AF and AF de novo.

## CONCLUSION

Oral anticoagulation substantially reduces the risk for ischemic stroke in patient with AF. Nevertheless, patients with AF may still have an ischemic stroke despite taking oral anticoagulants. This is often regarded as a treatment failure, whose mechanisms include non-compliance, reduced pharmacological efficacy of the anticoagulant in individual patients or other factors such as alternative stroke mechanisms (eg, small vessel occlusion). Anticoagulant therapy can be a challenging drug to manage, but if used appropriately it can be effective for the prevention of stroke associated with AF. Regular monitoring and good patient education are important for successful treatment.

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