Antithrombotic Treatment of Patients with Atrial Fibrillation and Ischemic Stroke

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Abstract

Objective: Assessment of the use of oral anticoagulants in patients with ischemic stroke and atrial fibrillation in the Republic of Moldova. **Methods:** A retrospective study of all patients hospitalized with stroke during one-year period in a municipal hospital. **Results**: Out of 735 patients with ischemic stroke, atrial fibrillation was noted in 28.4% (206/189). The majority were female, 57.8% (119/206) with the mean age of 70.1 ± 0.65 years. Ninety two (92.5%) of all patients had a high thromboembolic risk, 5.8% - medium and 1% - low risks. In the medium risk group the rate of antithrombotic treatment represented 88.9%. Even if about 92% were considered to have a high risk for thromboembolic complications, 60% were eligible for anticoagulation, but only 7.1% received it prior to the stroke. After the cerebrovascular accident all patients were considered to be at high risk, but only 14.8% were anticoagulated and only 26.6% (4/15) had the therapeutic International Normalized Ratio (INR) in the range 2.0-3.0. Physical disability and non-compliance were the most frequent reasons for noncompliance to anticoagulation. At the next visit 65.2% were receiving aspirin, and 20% were not receiving any antithrombotic medication. No hemorrhagic complications were reported after 14 months of follow up. **Conclusions:** A significant proportion of patients (92.9%) with atrial fibrillation and high antithrombotic risk were not anticoagulated before ischemic stroke for various reasons: underestimation of antithrombotic benefit and fear of hemorrhagic complications from physician's behalf and difficulties in systematic INR monitoring from patient's behalf.

Key words: atrial fibrillation, ischemic stroke, *antithrombotic* treatment.

Антитромботическое лечение больных с мерцанием предсердий, перенесших ишемический инсульт

Цель: определить процент применения непрямых антикоагулянтов (НАК) у больных с мерцанием предсердий (МП) и ишемическим инсультом. **Методы**: ретроспективное исследование всех больных с острым ишемическим инсультом, поступивших в одну городскую больницу, в течение одного года. **Результаты**: из 735 больных с ишемическим инсультом, МП было выявлено у 28,4% (206/735) больных среднего возраста (70,1 ± 0,65 лет), из которых большинство были женщины – 57.8% (119/206). Из всех больных 92,5% были с высоким тромбоэмболическим риском, 5,8% - средним и 1% - с низким. Процент назначения антитромботического лечения в группе больных со средним риском составил 88,9%. Из больных с высоким риском, в среднем 60% было показано назначение антикоагулянтов, но лишь 7,1% получили их до развития инсульта. После инсульта все пациенты считались с высоким тромбоэмболическим риском, но лишь 14,8% получали НАК, из которых 26,6% (4/15) поддерживали INR (2,0-3,0), тогда как реальные возможности получения антикоагулянтов было у 40,6% больных. Физическая нетрудоспособность и неспособность соблюдать рекомендации врача были самыми частыми причинами не назначения НАК. На повторном визите 65,2% больных получали аспирин, а остальные 20% не получали никакого антитромботического лечения. За 14 месяцев наблюдения не было зарегистрировано ни одного случая кровотечения. **Заключение**: значительная часть (92,9%) больных с МП и высоким тромбоэмболическим риском не принимали НАК до развития инсульта по разным причинам: недооценка преимуществ антикоагулянтной терапии, опасность геморрагических осложнений, необходимость регулярной проверки уровня антикоагуляции.

Ключевые слова: мерцание предсердий, ишемический инсульт, антитромбическое лечение.

Introduction

Atrial fibrillation (AF) is a common rhythm disturbance in the daily medical practice in Republic of Moldova. The most serious complication associated with AF is cerebral or systemic (non - cerebral) thromboembolism. This rhythm disturbance increases stroke risk 4-5 fold in any age group. Out of the total ischemic strokes, about 20-25% are cardioembolic and almost 60% of them due to AF, therefore, nearly 15% of the total number of ischemic strokes are due to AF. The annual rate of strokes in nonvalvular AF, without anticoagulant treatment, is 4.5% for the first thromboembolic event and 12% per year for recurrent events [1]. Thromboembolic risk is associated with an annual rate of systemic embolisms of about 0.3-0.8%, their frequency being substantially elevated in AF. Significant

and independent influence of AF on stroke risk is confirmed by the data of numerous randomized trials. Meta-analysis of multiple studies shows a reduction of approximately 68% in thromboembolic events on treatment with warfarin, in patients with AF [2]. Strokes due to AF have a more severe evolution than other forms of ischemic strokes, being associated with a higher mortality (nearly 30%) and a high rate of irrecoverable and invalidating neurological consequences [3].

Despite clinical evidence, several trials in USA and Europe showed that only 25-50% of patients with AF receive antithrombotic therapy corresponding to the risk [4]. The causes of this discrepancy between clinical practice and clinical trials are not easy to explain and it is not known whether the same situation is in RM.

In this work we have proposed as an aim to examine the use of anticoagulants and of the factors that influence it in patients with AF and ischemic stroke in a medical institution from the Republic of Moldova.

Material and methods

All patients with stroke, hospitalized in the hospital "SF. TREIME" from Chisinau have been studied retrospectively during the year of 2004. For inclusion in the study the patients have been identified in the data based on stroke from that hospital. At the first step of the research, the details on patients were obtained from the medical cards. The diagnosis of ischemic stroke was established beforehand by neurologists, and the ECG was evaluated by a cardiologist. The patients have been observed for 14.2 ± 0.74 months. The following information, during observation, was obtained through active examination in Institute of Cardiology; for immobile patients – at their homes, being completed by discussions with family doctors and relatives, also by the study of ambulatory medical cards.

Results

Seven hundred thirty-five patients with acute ischemic stroke were hospitalized during the study, 206 of the patients (28.4%) had AF confirmed through ECG. The characteristics of these patients at hospitalization are listed in tab. 1.

Table 1

**Characteristics of patients
with stroke and AF at trial inclusion**

Parameters	Patients with stroke and AF, n = 206
Age, years	70.1 ± 0.65
Women	57.8% (119)
Chronic atrial fibrillation	70.4% (145)
Arterial hypertension	87.4% (180)
Vascular pathology	82% (169)
Rheumatic valvulopathies	9.2% (19)
Congestive heart failure	96.1% (198)
Diabetes mellitus	29.1% (60)
Previous thromboembolic event	30.1% (62)
≥ 2 strokes	4.4% (9)
Period between strokes, months	27.2 ± 5.5
Mortality in the hospital	30.6% (63)

The mean age of subjects with AF was 70.1 ± 0.65 years (age range 34-91 years), the third part of them (29.1%) being aged ≥ 75 years. Among subjects with rhythm disturbances and stroke, more than a half was of female gender 57.8% (119). The great majority of patients with AF (84%) have suffered an established ischemic stroke.

The prevalence of AF in patients with stroke was 28.4%, and it varied depending on the type of cerebral ischemia, followed by transient ischemic attack (TIA) with 25%, lacunar stroke – 15.4% and minor stroke – 13.2%. Out of 206 patients with AF, chronic and persistent forms were present in 145 individuals (70.4%), paroxystic AF in 50 (24.3%) and atrial flutter in 11 patients (5.3%). It is notable, that 8 patients (3.9%) had AF, determined for the first time at hospitalization.

Cardiovascular pathology associated with atrial fibrillation increases the risk for stroke and aggravates its evolution, leading to the appearance of serious consequences. The detailed analysis of patients with ischemic stroke, in this trial, revealed the presence of associated diseases, which included associated cardiovascular pathology and diabetes mellitus, in most patients with AF (99.5%), with the exception of a man. Arterial hypertension was found in 87.4% of patients; vascular diseases, presented as stable angina pectoris, AMI, previous MI or diseases of peripheral vessels, were found in 88% of patients; cardiac failure of different grades - in 96.1% of patients; diabetes mellitus was found in 29.1% of patients, and 9.2% of subjects were diagnosed with rheumatic valvulopathy. A significant part of patients (30.1%) had previous thromboembolic events, in 4.4% of cases being multiple (≥ 2). The mean period between thromboembolic events lasted for 26.8 ± 2.6 months; 14.5% of patients have suffered a repeated stroke in less than a month from the anterior thromboembolic episode, and 61.3% individuals-in a year.

The patients were considered to be at high risk if at least 2 risk factors were identified by investigators for AF, in a meta-analysis of 5 randomized trials: (age > 75 years, hypertension, HF, diabetes mellitus) or ischemic stroke or previous TIA – $CHADS_2$ score, tab. 2.

Table 2

**The distribution of $CHADS_2$ score
and the evaluation of thromboembolic risk**

Points	Risk	AF + stroke n = 206	Deceased n = 63	Survivors n = 143
0	Low	2 (1.1%)	0%	2 (1.6%)
1	Moderate	12 (6.4%)	1 (1.7%)	11 (8.5%)
≥ 2	High	173 (92.5%)	57 (98.3%)	116 (89.9%)
RV	High	19 (9.2%)	5 (7.9%)	14 (9.8%)

RV- rheumatic valvulopathy.

The data included in the table show that most of the patients – 92.5%, have scored more than ≥ 2 points from the proposed score, which corresponds to a high thromboembolic risk with need for chronic therapy with oral anticoagulants, 5.8% of patients with AF presented a moderate risk, having the necessity of chronic treatment with antiaggregants or optional with warfarin and only about 1% of patients with AF did not have any risk factors for major thromboembolic events, being classified in the low risk group with aspirin considered sufficient for an adequate thromboembolic protection. A separate group was formed by 19 patients with rheumatic valvulopathy (9.2%) – pathology which implies a high thromboembolic risk and which constitutes an absolute indication for the administration of indirect anticoagulants, independently of the gained points according to CHADS2 score. Studying CHADS2 score in patients with AF it was noted that out of 12 patients with moderate risk, (8.3%) patients deceased, and out of patients of high risk 62 (32.3%) deceased, 5 (26.3%) of them suffering from rheumatic valvulopathies.

The examination of ambulatory medical cards at the 2nd research step (repeated examination) made possible the determination of the rate of prescribing antithrombotic treatment
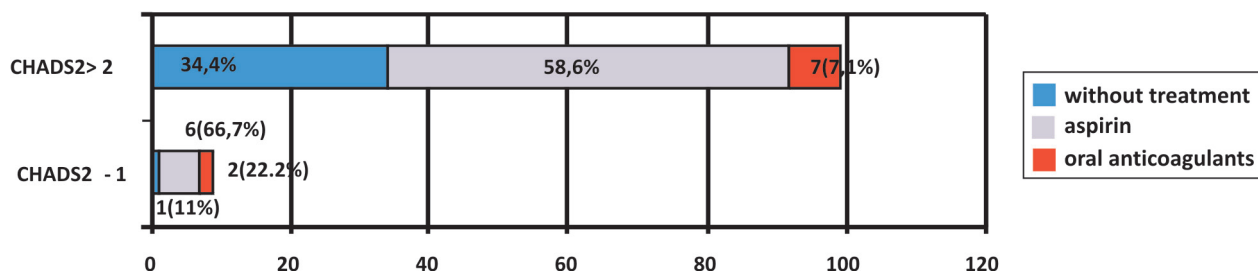
CHADS2> 2	34,4%	58,6%	7(7,1%)
CHADS2 - 1	6(66,7%)	2(22,2%)	1(11%)

Legend: without treatment / aspirin / oral anticoagulants

Fig. 1. The rate of antithrombotic medication in patients with different degrees of thromboembolic risk.

in the period before the certain thromboembolic event and gave the possibility to appreciate the extent of correspondence to guideline recommendations regarding this medication. The analysis of correlation between the risk evaluated by CHADS2 score and the applied antithrombotic treatment was possible in 108 patients examined repeatedly. As a consequence, it was concluded that none of these patients had a low thromboembolic risk, moderate risk was present in 9 patients (8.33%), and high risk for stroke had 99 patients (91.7%).

The rate of patients with moderate risk, administrating antithrombotic treatment corresponding to risk gradation constituted 88.9% (6 patients (66.7%) received aspirin and 2 patients (22.2%) – thrombostop). About 58 patients (58.6%), with CHADS2 score ≥ 2, administered antiplatelet drugs and only 7 patients (7.1%) had the benefit, before the stroke, of treatment with oral anticoagulants that corresponds to an adequate antithrombotic protection for this category of patients. The rate of antithrombotic treatment appreciated in dependence of the estimated risk for major thromboembolic events in patients with AF is represented in fig. 1.

Therefore, in the period before stroke, 99 (91.7%) patients had a high risk and absolute indications for the prevention with oral anticoagulants and only 9 (8.3%) patients had relative indications for anticoagulants use, presenting moderate thromboembolic risk. In this period, in ambulatory conditions, only 9 (8.3%) patients (7 of which had high risk, 2 of them moderate risk) administered preventive treatment with oral anticoagulants. Only 2 (1.8%) patients had PI in the recommended therapeutic range (40-60%), assuring an optimal antithrombotic protection, the other 7 patients presented values of PI greater than 60%. INR index was not determined in any patient. In the group of patients with valvular AF only 4 patients received indirect anticoagulants. The other 10 patients with AF and mitral valve stenosis remained unprotected, the antithrombotic treatment lacking in the ambulatory medical card.

After discussions with the family doctors and the study of medical documentation it was appreciated that only 64 (59.3%) patients had real possibilities to receive indirect anticoagulants, and regarding the rest of them: 17.6% were incompliant, 7.4% did not have the possibility to monitor coagulation parameters having an advanced grade of disability, 11.1% had uncontrolled hypertension, 3.7% - gastrointestinal pathology with high bleeding potential, and a patient (0.9%) had previously a major hemorrhagic episode, tab. 3.

Table 3

Contraindications for administration of oral anticoagulants

Contraindications	Before stroke, n = 108	After stroke, n = 101
Lack of compliance	17.6% (19)	27.7% (28)
Great disability	7.4% (8)	15.8% (16)
Uncontrolled hypertension	11.1% (12)	4.9% (5)
Gastrointestinal pathology	3.7% (4)	5.9% (6)
Previous bleedings	0.9% (1)	1% (1)
Recent stroke	-	2% (2)
Oncological pathology	-	2% (2)
Real possibilities to receive oral anticoagulants	59.3% (64)	40.6% (41)

Treatment with aspirin was received by 64 (59.3%) patients (6 with moderate risk and 58 with high risk). Absolute contraindications had only a patient with gastrointestinal acute pathology associated with recidivating bleedings. Six (5.6%) patients presented relative contraindications for aspirin, having gastrointestinal pathologies, and a patient presented allergic reaction to non-steroid anti-inflammatory drugs. After the preventive treatment, 2 patients presented exacerbations of gastrointestinal pathology, and a woman had a hemorrhagic episode.

In this way, based on the received results it can be stated that out of 108 patients who needed antithrombotic treatment, only 14% administered antithrombotic medication in accordance with the risk, in the period before thromboembolic events that is shown in fig. 2.

According to CHADS$_2$ score, all patients evaluated repeatedly were included in the group of patients with high thromboembolic risk and had absolute indications for the administration of oral anticoagulant therapy. Only 15 (14.85%) patients with stroke and AF have been recommended and were administering anticoagulant therapy, only in 4 (3.96%) patients PI reached the target values of (40-60%) and INR 2.0-3.0, in this way being protected by repeated thromboembolic events, the data being graphically presented in fig. 3.

Analyzing the indications, contraindications, degree of physical disability of patients, possibility of PI monitoring in policlinics conditions and patient compliance, real possibilities of antithrombotic preventive treatment were appreciated for only 41 (40.6%) of interrogated patients, the rest of them: 28 (27.7%) were incompliant to treatment, 16 (15.8%) had marked physical disabilities, 6 (5.9%) presented exacerbations of gastrointestinal pathology, 5 (4.95%) had uncontrolled hypertension, 1 patient had an acute bleeding, 2 patients had
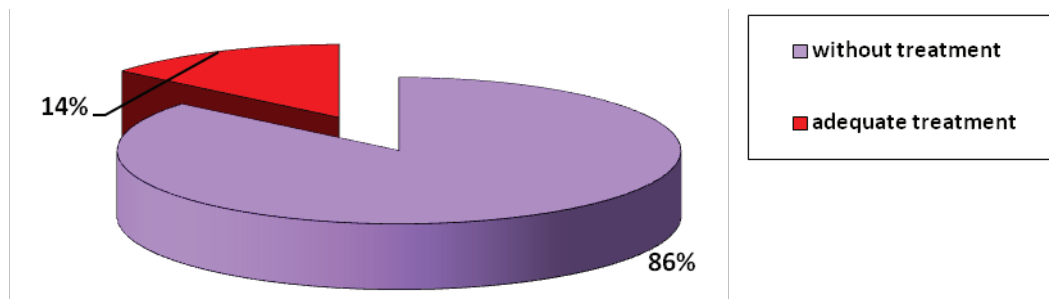
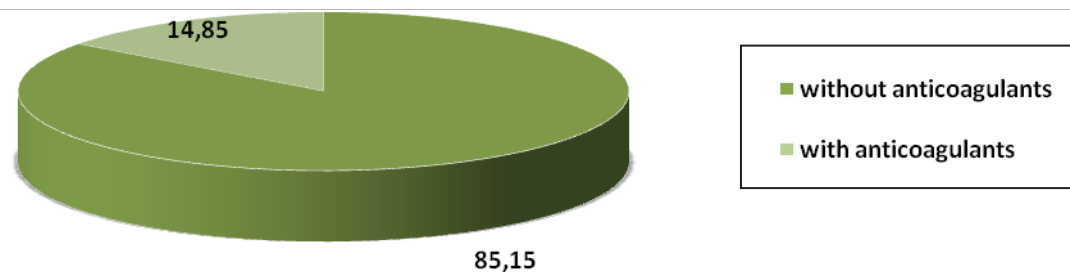Fig. 2. The rate of adequate antithrombotic treatment.

Fig. 3. The rate of patients who received anticoagulants at repeated examination.
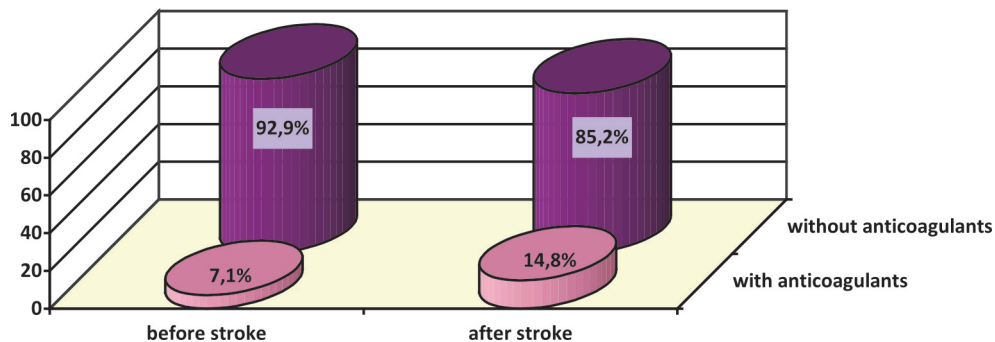

Fig. 4. The rate of oral anticoagulant treatment.

repeated stroke during the first month after previous stroke, and in 2 patients oncological pathology was suspected.

Sixty-six (65.3%) patients were administered aspirin, and a patient received clopidogrel. Nine patients did not receive aspirin because of gastrointestinal pathology, a patient presented allergy to aspirin, and 25 patients did not use antiaggregants, in this way ignoring medical indications, or because of the fact that such recommendations were not accepted, or administered irregularly antiplatelet therapy. It is notable that, aspirin was administered to 67.5% of the patients with chronic AF and 15.8% with paroxystic AF, and oral anticoagulants were administrated only to patients with chronic form of AF. On background treatment with antithrombotics 2 patients developed complications of mild and moderate gravity: a patient presented gastrointestinal bleeding, and another one developed acute erosions of gastric mucosa being on aspirin.

Therefore, after repeated stroke the rate of therapy with oral anticoagulants increased 2-fold, but it still remained

insufficient in patients with AF and at high thromboembolic risk, fig. 4.

During observation period (14.2 ± 0.74 months) the rate of thromboembolic recurrences was 29.6% (37/125), and of late deaths – 35.2% (44/125). In this period no hemorrhagic complications as a consequence of oral anticoagulant therapy administration were registered.

Discussions

Atrial fibrillation is the most common rhythm disturbance in clinical medical practice. Annual incidence of stroke is 6-fold higher in patients with AF, comparative to individuals of similar age and sinus rhythm [5]. Many randomized trials have shown the efficacy of anticoagulants in preventing stroke in patients with AF [4]. In a general analysis on AF the investigators have shown that warfarin significantly reduces thromboembolic risk, from 4.5% to 1.45% annually, with relative risk reduction by 68% [6]. The benefic effect of warfarin has been obtained with a minimal risk elevation for

hemorrhagic complications, 1.2% in comparison with 1% for placebo. In absolute terms approximately 90 ischemic strokes are prevented, if 1000 patients with high risk are treated during 1-year period.

Recently guidelines and articles have been published on anticoagulation in AF. In clinical practice the rate of anticoagulant use still remains to be suboptimal. The frequency of oral anticoagulant use in patients without contraindications varies between 15.2 and 78.8%, warfarin being prescribed more often to young patients (< 65 years) [7]. Our study confirms these observations and adds information on circumstances which affect the clinic decision making regarding anticoagulant administration.

Our results show a resistance in use of indirect anticoagulants in patients with AF and high thromboembolic risk, with only 7.1% prescriptions before stroke. The retrospective nature of the study makes the evaluation of reasons difficult, though the registration of contraindications for oral anticoagulants was not evident at the examination of medical cards. These data are lower than the results of Kalro et al. trial in Great Britain. They reported that only 31% of patients with AF, for at least 12 months, with a major risk factor, were anticoagulated at the moment of enrollment in the study [8]. In addition, Jackson et al. have reported similar data in Tansania, with only 34% patients with AF with high risk who received warfarin [9].

Why not is warfarin used enough, despite important arguments which support its benefit in AF? One of the possible reasons is that clinical trials are not considered representative for "the real world", with a greater rate of men and younger patients. Because of monitoring difficulties the patients often refuse the administration of warfarin. These refusals have been documented rarely in the studied medical cards, being found only for 1.2% patients. The physicians can also be reserved in the initiation of treatment with warfarin, because of the time lost in order to make the patient understand why and in which way to administer this drug. Some specialists even doubt the application in their daily practice of the recommendations from guidelines.

The apparent lack of trust of physicians in treatment with warfarin, in patients with AF, can be partially explained through exaggerated care of hemorrhagic risks and underestimation of stroke risk. Another reason is that the guideline for the management of patients with AF, which was valid in 2004, presented relatively other indications for anticoagulation. In fact, the lack of knowledge on recommended antithrombotic therapy can partially explain why the patients treated in neurological departments had fewer chances to receive oral anticoagulation. There is still the possibility of some underestimations regarding the real number of patients with contraindications for anticoagulation.

After discussions with the family doctors and examination of medical documentation it has been appreciated that only 64 (59.3%) patients had real possibilities to receive indirect anticoagulants, and 17.6% were incompliant, 7.4% did not have the possibility to monitor coagulation parameters,

having an advanced degree of disability, 11.1% had uncontrolled hypertension, 3.7% - gastrointestinal pathology with high bleeding potential, and a patient (0.9%) had previously a major hemorrhagic episode.

Unified analysis of 5 major randomized trials has shown that advanced age is an independent risk factor for stroke [6]. The risk for stroke in AF starts to increase from the age of 65 years, though, it is clear that the risk for stroke is significant in those ≥ 75 years, who have a greater benefic effect at administration of vitamin K antagonists, comparative to the effect of aspirin [10, 11]. With aging, the relative efficiency of antiplatelet medication in preventing stroke reduces in patients with AF, which does not happen with oral anticoagulants. AF is the most frequent reason of a disabilitating stroke in elderly women [4]. The resistance of physicians in starting oral anticoagulants in elderly patients is generally considered to be related to a higher risk for hemorrhagic complications. The investigators from SPAF II trial have shown that the risk of major bleeding was substantially higher in patients with AF > 75 years, comparative with younger patients, who received anticoagulation therapy at the same extent [4]. Unlike this one, the unified analysis of 5 trials demonstrated only a single intracerebral bleeding among 223 patients of more than 75 years, who received warfarin [6]. But it is known the fact that the incidence of intracerebral bleeding increases with ageing, even in people who do not use oral anticoagulants. It is possible, that the elevated risk for intracerebral bleeding in the elderly could be caused not by warfarin administration, but by physiological changes in the coagulation process happening with ageing [12]. Although our study group was small, there were not reported any hemorrhagic complications in an observational period of 14.2 months.

In the case of initiation of warfarin therapy it is important to obtain the therapeutic level of anticoagulation (INR 2.0-3.0). Recent guidelines recommend a lower intensity of anticoagulation in patients > 75 years, with INR 2.0 [13]. INR level has to be intensely monitored in the elderly patients, in order to minimize not only the risk of oral anticoagulants over dosage, but also of suboptimal therapy, in which the protection for thromboembolic events is lower [14]. In our trial, at the moment of hospitalization, only 2 out of 9 patients on oral anticoagulants had INR within the range 2.0-3.0, and at repeated examination - 4 of 15.

Finally, it is important to mention that a significant proportion of our patients have initiated anticoagulation after stroke. The reason for this change in the management of patients at high risk before the event is not entirely clear, although individual differences can exist in medical practice.

Evaluating the indications, contraindications, physical capacities of patients, as well as technical conditions of policlinics, it has been determined that only 40.6% of reevaluated patients after stroke had real possibilities to administer preventive antithrombotic treatment. Among those who did not receive oral anticoagulation therapy – 27.7% were absolutely incompliant to treatment, 15.8% had marked physical disabilities, 5,9% presented exacerbation of gastrointestinal

pathology, 4,9% had uncontrolled hypertension, 1 woman suffered from frequent metrorrhagies, 2 patients have recently had acute stroke, and 2 patients were suspect for oncologic pathology. In 65.3% patients aspirin was recommended.

In the future, through inclusion of some additional factors it may be possible to determine a more exact rule for appreciation of thromboembolic risk. For example, systolic dysfunction of the left ventricle found at trans-thoracic 2D Echo-CG is an independent risk factor for stroke in AF [15]. It is also probable that hormonal substitutive therapy [16] and smoking [15] increase risk for stroke in AF, while moderate alcohol consumption reduces it [16]. Finally, the next studies will determine whether the biologic markers of inflammation (for ex. C-reactive protein) or endothelial dysfunction (for ex. von Willebrand factor) could help clinicians in risk prediction in the population with AF and ease the decision to initiate oral anticoagulant therapy.

In conclusion, despite of the limitations of a small retrospective single-centered trial, our data show that anticoagulant therapy is insufficiently used in patients with AF and high thromboembolic risk, in Republic of Moldova. The reasons are not clear, but in practical conditions, medical science based on evidence is not always applicable. Recent data confirm the benefits of anticoagulation in conditions outside of trials. Therapy with warfarin needs to be considered in all patients with AF and high thromboembolic risk, and advanced age itself should not be referred to as an absolute contraindication for oral anticoagulation.

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