SECONDARY PREVENTION IN PATIENTS WITH ATRIAL FIBRILLATION AND STROKE OR TRANSIENT ISCHEMIC ATTACK – AN INSIGHT FROM THE FACTS PROGRAMME

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ABSTRACT

Background. Cardioembolic stroke secondary to atrial fibrillation (AF) accounts for 1.5%-23.5% of all ischaemic strokes. Patients with prior stroke or transient ischaemic attack (TIA) are at high risk for stroke recurrence. Prognosis for patients with AF related stroke is worse than those with other types of stroke.According to the current guidelines secondary prevention in these patients should be based on anticoagulant therapy.
Aim of the study. The purpose of this analysis is to evaluate the extent of anticoagulation in clinical practice in patients with previous stroke or TIA.
Methods. We have evaluated records obtained from the FACTS registry. We included 374 patients with AF and a history of stroke or TIA,from different areas of Romania, and collected data regarding antithrombotic therapy.
Results. According to CHADS2 all patients were at high risk and should receive anticoagulation therapy. In our group 51,37% were treated with OAC alone and 15,77% with OAC in combination with antiplatelet therapy. Of OAC the most used drug was acenocoumarol and optimal anticoagulation (INR between 2 and 3) was found in 68% patients. There were no differences between genders and OAC prescription was not influenced by AF type. OAC was preferred in 68.52% patients with high bleeding score (HASBLED > 3).
Conclusion. The main finding of the analysis was that adherence to guidelines recommendation concerning AF patients with previous stroke/TIA is still low.However,patients at high risk for stroke recurrence and high bleeding score were mostly treated according to current recommendations, suggesting that there is an increasing awareness and adherence to current clinical guidelines.

Key words: atrial fibrillation, stroke, oral anticoagulation therapy, adherence, guidelines

INTRODUCTION

Of cardiac arrhythmias atrial fibrillation (AF) is responsible for the most hospitalizations and increases the risk of ischemic stroke by approximately five-fold (1). Patients with stroke secondary to AF have more severe strokes and a worse prognosis than patients with sinus rhythm (2). Epidemiological data show 1 in 6 people around the world will have a stroke during their lifetime (3,4). AF is responsible for 1.5-20% of all ischemic strokes in patients age 60 and older (1).The use of anticoagulation in patients with AF and stroke risk factors reduces the risk by two-third whilst antiplateletsalone reduce itonly by one-fifth (5,6).

Several stroke risk stratification charts for patients with AF were developed over the years based on analysis from different clinical trials. They aim to identify patients at high risk of stroke who will benefitfrom the anticoagulant therapy. The most widely accepted risk scorein the recent guidelines of management of AF is $CHADS_2$ score (7). This is a simple point-based, practical and relatively accurate score (8): 1 point is assigned to congestive heart failure, hypertension, age over 75 years and diabetes and 2 points are given for previous stroke

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or transient ischemic attack. Maximum of points is six and patients are divided in three risk groups: low-risk patients - those with 0 points, moderated-risk patients with 1 or 2 points and high-risk patients with score above 3 and for this group anticoagulation therapy is strongly recommended. Nevertheless patients with 0-1 points are not all 'low-risk' and in the effort to improve stroke risk stratification schema and taking into account more recent evidence of 'new risk factors'an updated risk stratification score was validated.CHA_2DS_2VASc (9) is the most recent risk stratification score and can identify truly low-risk patients who do not require anticoagulant therapy. CHA_2DS_2VASc is an extension of $CHADS_2$ and includes 1 point for vascular disease (previous myocardial infarction, peripheral artery disease or aortic plaque), female gender and for age ≥ 65 years and in addition to original schema 2 points are given for age ≥75 years. Maximum score is 9 points. The truly low-risk patients in which anticoagulation therapy showed no benefit are those with CHA_2DS_2VASc = 0 and women under the age of 65 (10,11). For patients with CHA_2DS_2VASc ≥ 1 anticoagulation should be considered (12).

OAC comes with a bleeding risk especially in older patients who are also at high risk for stroke. Assessment of bleeding risk is recommended (12) for every patient before starting anticoagulation and HAS-BLED score was proposed. This simple point-based clinical score consists in adding 1 point for each of the following: hypertension, abnormal renal and liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs and alcohol consumption, with a maximum of 9 points. Also, this score helpsthe clinicians to identify correctable bleeding risk factors such as uncontrolled hypertension or the necessity of antiplatelets association. A score ≥ 3 is associated with a high bleeding risk but does notrepresent a contraindication for oral anticoagulation use. Actuallythe patients in this group benefit more from anticoagulation therapy (10).

Anticoagulation with vitamin K antagonists is highly effective in preventing embolic events in patients with AF and currently they are the most commonly used drugs in primary or secondary prevention. In the past few yearsnovel anticoagulant agents such as direct thrombin inhibitors (dabigatran) and factor Xa inhibitors (apixaban, rivaroxaban) have been approved as well for prevention of stroke in these patients. Compared to warfarin they reduce overall and cardiovascular mortality, stoke and systemic embolism, major and intracranial bleeding (13). OAC has proven efficacy in prevention of recurrent stroke but despite this and the clear recommendations in the guidelines (12,14) patients with AF and prior stroke or transient ischemic attack are stillundertreated. The level of treatment for patients with AF and prior stroke or TIA reported by several studies is under 60% of eligible patients (15).

The aim of the present study was to provide an overview of anticoagulation in patients with AF and prior stroke or transient ischemic attack and which are treated according to the current guidelines recommendations on oral anticoagulation.

METHODS

All patients with AF and prior ischemic stroke or transient ischemic attack were selected from the large group of patients with AF included in the FACTS (Atrial **F**ibrillation-**A**wareness, **C**onsciousness and **T**herapeutic **S**trategy)[16] Database. The FACTS spot-registry is a part of FACTS programme started in 2010 in order to assess the unfortunateimpact of suboptimal AF awareness in Romania on AF management translated into insufficient treatment and stroke prevention. Twenty-seven cardiology units located in different regions of Romania recruited patients over 18 years with any type of atrial fibrillation or atrial flutter present at the time of enrollment or documented during the past 12 months. The recruitment period was one year.

STATISTICAL ANALYSIS

Univariate analysis was performed to describe population: categorical variables were described using absolute frequencies and proportions, while continuous variables were summarized by means and standard deviations.For bivariate analysis we used chi-squared test for categorical variables and t-test or Mann-Whitney test for interval variables. Statistical significance was set at *p-value* less than 0.05. All analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY).

RESULTS

Patients were recruited between March 2011 and April 2012. Our study group included 374 patients with a history of stroke or transient ischemic attack. The basal characteristics of these patients are shown in Table 1 and were reported in a previously published work[17].We further analyze the extent of antithrombotic therapy in this group of patients.

TABLE 1. *Patients basal characteristics*

	Stroke/TIA+ (n = 374)	Stroke/TIA- (n = 3326)	p-value
Age	71.71 ± 9.988	69.84 ± 11.304	**0,0022**
Abdominal obesity	166 (10.9%)	1354 (89.1%)	**<0.0001**
Hypertension	348 (13.0%)	2337 (87.0%)	**<0.0001**
Grade I	15 (13.6%)	95 (86.4%)	**<0.0001**
Grade II	156 (11.6%)	1189 (88.4%)	**<0.0001**
Grade III	152 (14.1%)	925 (85.9%)	**<0.0001**
*not mentioned	121 (10.4%)	1047 (89.6%)	**<0.0001**
Sedentary lifestyle	198 (12.3%)	1410 (87.7%)	**<0.0001**
Dislipidemia	174 (11.0%)	1407 (89.0%)	**<0.0001**
Total cholesterol	131 (10.9%)	1072 (89.1%)	**<0.0001**
LDL-cholesterol	33 (8.7%)	345 (91.3%)	**<0.0001**
HDL cholesterol	71 (11.1%)	571 (88.9%)	**<0.0001**
Triglycerides	59 (10.2%)	518 (89.8%)	**<0.0001**
Diabetes	118 (12.4%)	832 (87.6%)	**<0.0001**
Smoking	99 (12.0%)	723 (88.0%)	**<0.0001**
Alcohol consumption	33 (8.8%)	343 (91.2%)	**<0.0001**
Associated diseases			
Cardiovascular associated diseases	425 (12.4%)	3016 (87.6%)	**<0.0001**
Coronary artery disease	206 (12.6%)	1434 (87.4%)	**<0.0001**
Myocardial infarction	75 (16.7%)	375 (83.3%)	**<0.0001**
Acute coronary syndrome	35 (10.4%)	302 (89.6%)	**<0.0001**
Angina pectoris	65 (9.9%)	594 (90.1%)	**<0.0001**
Silent ischemia	57 (14.0%)	350 (86.0%)	**<0.0001**
History CABG[1]/PCI[2]	24 (13.6%)	152 (86.4%)	**<0.0001**
Heart failure	344 (12.5%)	2403 (87.5%)	**<0.0001**
NYHA** class I	5 (11.6%)	38 (88.4%)	**<0.0001**
NYHA class II	138 (11.8%)	1034 (88.2%)	**<0.0001**
NYHA class III	161 (13.2%)	1060 (86.8%)	**<0.0001**
NYHA class IV	36 (12.5%)	253 (87.5%)	**<0.0001**
*not mentioned	104 (10.7%)	871 (89.3%)	**<0.0001**
Valvulopathy	281 (11.8%)	2106 (88.2%)	**<0.0001**
Valvularprosthesis	30 (11.5%)	232 (88.5%)	**<0.0001**
Valvular heart disease – mitral stenosis	43 (15.2%)	240 (84.8%)	**<0.0001**
Valvular heart disease – aortic stenosis	41 (11.2%)	325 (88.8%)	**<0.0001**
Valvular heart disease – mitral regurgitation	232 (11.5%)	1793 (88.5%)	**<0.0001**
Valvular heart disease – aortic regurgitation	97 (13.7%)	611 (86.3%)	**<0.0001**
Dilated cardiomyopathy	92 (13.4%)	594 (86.6%)	**<0.0001**
Hypertrophic cardiomyopathy	46 (11.4%)	357 (88.6%)	**<0.0001**
Peripheral arterial disease	43 (22.2%)	151 (77.8%)	**<0.0001**
Sinus node disease	36 (18.5%)	159 (81.5%)	**<0.0001**
Non-cardiovascular associated diseases			
COPD***	37 (9.0%)	374 (91.0%)	**<0.0001**
Hyperthyroidism	10 (11.9%)	74 (88.1%)	**<0.0001**
Hypothyroidism	12 (12.0%)	88 (88.0%)	**<0.0001**
Chronic kidney disease	89 (13.5%)	572 (86.5%)	**<0.0001**
Malignancy	14 (11.4%)	109 (88.6%)	**<0.0001**
Other	207 (11.1%)	1654 (88.9%)	**<0.0001**
CHADS2 Score	4.26 ± 0.866	2.06 ± 0.919	**<0.0001**
CHA2DS2VASc Score	5.55 ± 1.545	3.43 ± 1.534	**<0.0001**
Atrial fibrillation in the evaluation	243 (10.1%)	2165 (89.9%)	**<0.0001**
Atrial fibrillation in the past year	355 (10.2%)	3112 (89.8%)	**<0.0001**
Atrial flutter in the evaluation	14 (6.1%)	217 (93.9%)	**<0.0001**
Atrial flutter in the past year	22 (8.1%)	251 (91.9%)	**<0.0001**

*not mentioned – no grade/class was mentionated
**NYHA – New York Heart Associati on classificati on
***COPD – chronic obstructive pulmonary disease
[1]CABG – coronary artery bypass graft
[2]PCI – percutaneous coronary interventi on

The available antithrombotic in Romania at the time of the survey were:acenocumarol, warfarin, dabigatran, clopidogrel, and aspirin. We mention that warfarin is approved in our country but is not widely available and dabigatranhadonly recently-been approved at that time.

OAC (acenocoumarol, warfarin or dabigatran) alone was used in 51.87% of the patients in our group and the preferred OAC was acenocoumarol. Patients were also treated with antiplatelettherapy alone (11.49% with aspirin, 2.4% with clopidogrel) or in association with vitamin K antagonist (13.10% aspirin+acenocoumarol, 2.67% clopidogrel + acenocoumarol). 3.2% had triple therapy (OAC + aspirin + clopidogrel) and 6.41% were taking double antiplatelet therapy. The use of different ofantithrombotictherapy schemas is shown in Figure 1 and their use in relation with $CHADS_2$ score in Figure 2.

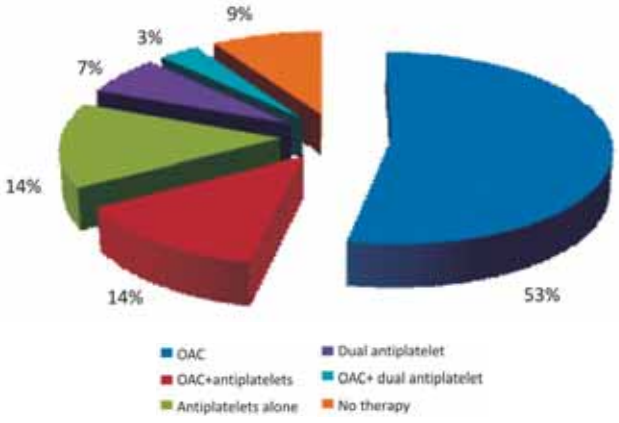

FIGURE 1. *Type of antithrombotic therapy*

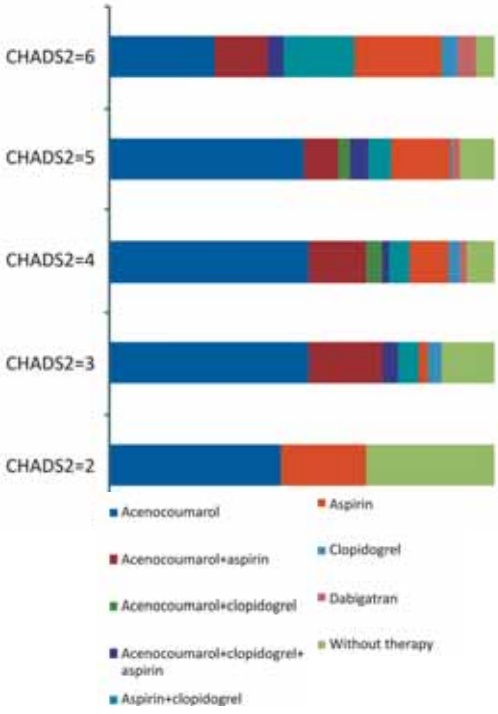

FIGURE 2. *Type of antithrombotic therapy according to $CHADS_2$ score*

The distribution of patients with or withoutOAC in relation to thromboembolic risk according to $CHADS_2$ score is reported in Figure 3.

Bleeding risk assessment was performed using the HAS-BLED score. No patients had a bleeding score higher than 7 (Figure 4) and the calculated mean value for HAS-BLED depending on $CHADS_2$ score shows a slight increase for bleeding risk with increasing stroke risk (Figure 5). OAC therapy was prescribed in 68.52% patients in the high risk group (HAS-BLED > 3) and in 80.48% patients with low bleeding risk.In the high bleeding risk group antiplatelets alone were present in 15.53% patients and 8.76% were taking dual antiplatelet therapy (Figure 6).

We found no difference in gender or age in patients receiving or not OAC, and OAC prescription was not influenced by the HAS-BLED score (OR=0.795 CI 95%: 0.507-1.245 p= 0.315.) or the type of AF (OR=0.937 CI 95%: 0.168-1.185, p=0.103).

Median value for international normalized ratio (INR) was 2.265 and 68% patients taking vitamin K antagonist were at optimal level of anticoagula-

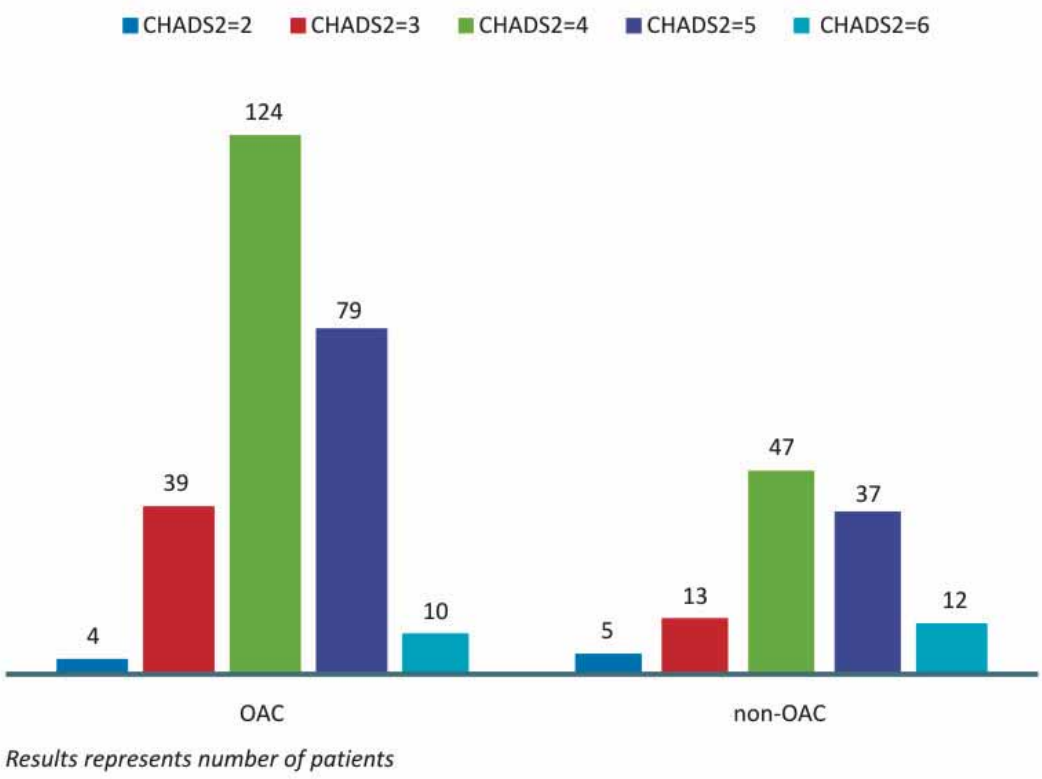

FIGURE 3. *Patients with prior stroke/TIA and oral anticoagulant treatment categorised by $CHADS_2$ score.*

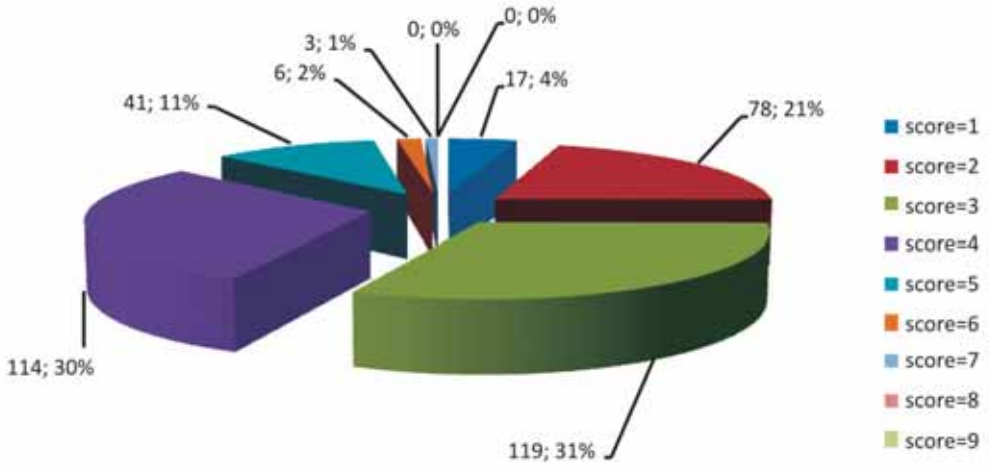

FIGURE 4. *HAS-BLED score in patients with previous stroke*

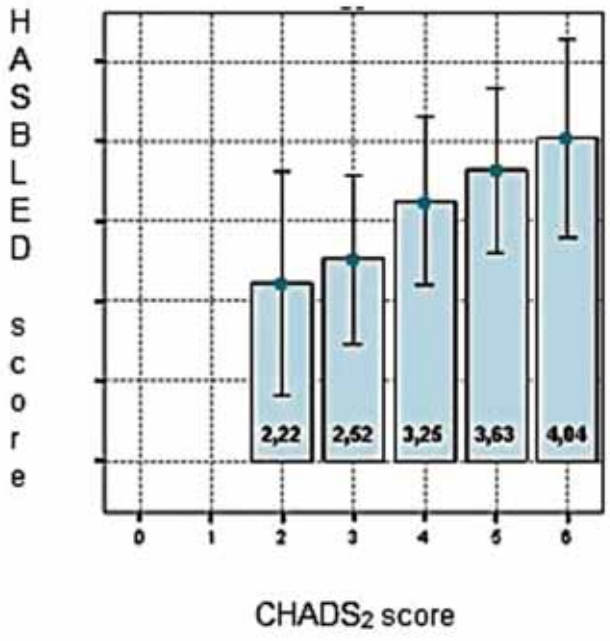

FIGURE 5. *Mean value for HASBLED score and $CHADS_2$ score*

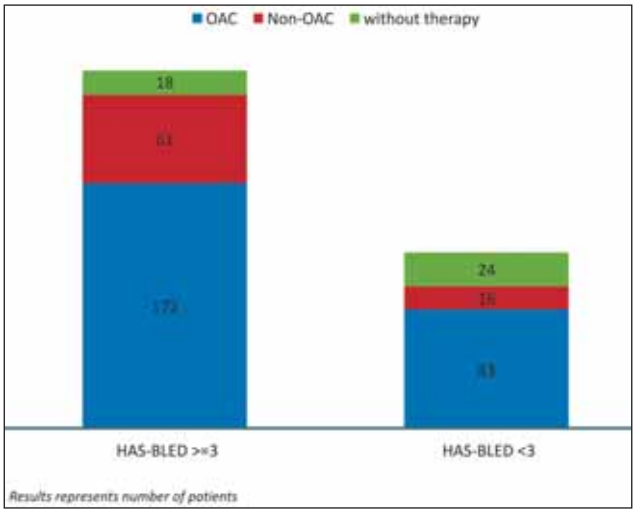

FIGURE 6. *Antithrombotic therapy and HASBLED score.*

tion (INR values between 2 and 3) with monthly or even more frequent control in 65% of those, but time in therapeutic range (TTR) was not routinely calculated. Two thirds of patients with high bleeding risk were optimallyanticoagulated and had monthly or more frequent INR assessments.Significant differences in mean INR values were found between patients with frequent control and those with more than 4 weeks interval. ($p < 0.001$)

DISCUSSIONS

This study analyzed the rate of adherence to OAC therapy for patients with risk of stroke recurrence. The main finding was that adherence to guidelines recommendation for patients with stroke/TIA history is still low. But prescription rate in this group were similar to those reported in Europa for stroke prevention in patients with AF[18].The underuse of OAC in clinical practice with respect of current guidelines recommendation was reported in different studies from several countries. Less than 70% of patients with $CHADS_2 \geq 2$ were receiving OAC (15) and 43% of those with prior AF related stroke admitted for stroke recurrence did not receive OAC, 68% of those who received warfarin were under-anticoagulated and 15% were not taking any antithrombotic therapy (19).

In our groupa high percent of patients with high bleeding risk scores were receiving OAC. This findingdemonstrated that despite some resistance in the use of OAC, patients at high risk for stroke recurrence and high bleeding score were treated according to current recommendations suggesting that there is an increasing trend in knowledge and higher adherence to present clinical guidelines. Optimal anticoagulation in patients with OAC was found in 68%, a rate similar to that recently reported in patients with OAC for stroke prevention from Italy (20). OAC prescription was not statistically influenced by the AF typein our study probably because permanent AF is more prevalent in ourgroup of patients, and the belief in clinical practice is to anticoagulate mainly the patients with chronic type of AF. (21)

Further data from FACTS Database will need to be analyzed in order to provide a more accurate picture regarding the use OAC therapy in secondary stroke prevention and also to bring a global image for OAC therapy in Romania.

CONCLUSIONS

The main finding of the analysis was that the adherence to guidelines recommendation concerning anticoagulation therapy for secondary prevention in patients with atrial fibrillation andprevious stroke or transient ischemic attack is still low.However, we also found that patients at high risk for stroke recurrence and high bleeding score were treated according to current recommendations, suggesting that there is an increasing awareness and higher adherence to current clinical guidelines

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