

Official study Title (Full):

ASSESSMENT OF ADHERENCE TO NEW ORAL ANTICOAGULANTS IN ATRIAL FIBRILLATION PATIENTS WITHIN THE OUTPATIENT REGISTRY PROFILE. PROSPECTIVE OBSERVATIONAL STUDY (ANTEY study)

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Unique Protocol ID: ANTEY

Brief Title: Assessment of Adherence to New Oral anticoagulants in Atrial Fibrillation patients Within the Outpatient registry (ANTEY)

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Primary Study Objective(s) Primary study objective

The aim of the present study is to assess adherence to therapy and factors associated with adherence in patients with CV disease complicated by non-valvular atrial fibrillation requiring OAC treatment within the outpatient registry PROFILE (prospective, observational study).

1. Data collection in patients with non-valvular atrial fibrillation requiring OAC treatment included in the registry
2. Evaluation of actual patient adherence to OACs

Secondary Study Objective(s)

1. Evaluation of potential patient adherence to OACs
2. Determination of most significant factors associated with adherence to OACs in patients with non-valvular AF
3. Validation of new original 5-item Questionnaire
4. Evaluation of doctor's adherence to OAC prescription according Guidelines (ESC). Management of atrial fibrillation,2016)

Study Type and Design

Prospective non-interventional single-center study aimed to evaluate actual adherence of AF patients using the 8-item Morisky Medication Adherence Scale.

AF patients from ongoing PROFILE registry will be invited to visit the scientific center.

2 visits with a 6-month interval are expected for each patient as part of routine clinical practice and phone contact is scheduled for each patient 1 year from the first visit to scientific center (follow-up period).

Study operational /organizational aspects

Study Location – State Research Center for Preventive Medicine

Population and methods

Study Population

Primary patients with non-valvular atrial fibrillation included in the outpatient registry PROFILE during the period 01.01.2011–31.08.2015.

Note:

At the moment (from 2011 to 2015) there are 225 atrial fibrillation patients included into PROFILE registry.

Taking into account that 100% may not be available to complete the study the optimal amount of patients should be considered as 200

Sample size has been estimated on expected patients' availability to contact. The observed CI would be (42.9-57.1) if the adherence rate was as observed in the study with lowest observed rate (50%), and (85.0-93.8) if the rate was as observed in the study with the highest observed rate (90%)

Adherence rate actual	95% Confidence interval
180/200 (90%)	85.0 - 93.8
160/200 (80%)	73.8 - 85.3
140/200 (70%)	63.1 - 76.3
120/200 (60%)	52.9 - 66.8
100/200 (50%)	42.9 - 57.1

1. Martsevich S.Yu.1, Loukianov M.M.1, Kutishenko N.P.1 REPORT ON THE ROUND-TABLE MEETING: "REGISTERS IN CARDIOLOGY: THE BASIC RULES OF MANAGEMENT, MODERN EXPERIENCE AND THE RESULTS OF THEIR CREATION IN THE VARIOUS REGIONS OF THE RUSSIAN FEDERATION": (In Russian)

2. Lukina Y.V., Martsevich S.Y., Zagrebelnyi A.V., Tripkosh S.G., Aidu F.A., Deev A.D. THERAPY COMPLIANCE IN AMBULATORY PATIENTS: PROFILE REGISTRY DATA. Cardiovascular Therapy and Prevention. 2013;12(5):56-61. (In Russian)

Inclusion Criteria (detailed)

- Men and women above 18 years of age who were included in the PROFILE registry by the start of the observational study
- Presence of written informed consent to participate in the study, fill in the study questionnaires and have personal data analyzed
- Presence of any form of non-valvular atrial fibrillation with CHA2DS2-VASc score of ≥ 1 or patients with CHA2DS2-VASc score = 0, who are already taking OAK

Exclusion Criteria

Patients with high bleeding risk, including patients with:

- Congenital or acquired bleeding disorders
- Uncontrolled resistant hypertension
- Exacerbation of gastric and duodenal ulcer
- Vascular retinopathy
- Recent history of intracranial or intracerebral hemorrhage
- Pathology of the brain and spinal cord vessels
- Recent history of brain, spinal cord or eye surgery
- History of bronchiectasis or pulmonary hemorrhage

- A CHA2DS2-VASc score of 0 (OACs are not indicated)
- Pregnancy, lactation
- Planned surgery
- Known hypersensitivity to ingredients of medications used in the study

Safety will be assessed by collection and summarizing of AEs, SAEs, deaths, laboratory results and vital signs to study treatment. At each study visit, nondirective questioning will be used to elicit AE reports from patients. All AEs and SAEs, whether volunteered by the patient, discovered by study site personnel during questioning, or detected by examination, laboratory testing, or other means, will be recorded in the patient record and case report forms. Safety analyses included all patients receiving ≥ 1 dose of study treatment. Patients will be analyzed according to actual treatment received.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

All AEs including but not limited to events reported by the patient, or reported in answer to an open question by the Masked Investigator or delegated staff member, which fall into any of the above definitions must be recorded as an AE and should include the following information:

SEVERITY

Severity describes the intensity of an event, and will be assessed as:

Mild

The AE does not interfere in a significant manner with the patients normal functioning level. It may be an annoyance.

Moderate

The AE produces some impairment of function but not hazardous to health. It is uncomfortable and/or an embarrassment.

Severe

The AE produces significant impairment of functioning or incapacitation and/or it is a hazard to the patient.

If an AE changes in severity, the worst severity should be reported.

Concomitant Treatment(s)

Concomitant treatment will be prescribed according to real-life clinical practice. All medications for treatment of concomitant diseases taken by patients at study entry and all additional drugs will be considered concomitant therapy and will be recorded in patients' cards.

Prohibited drugs

According to routine clinical practice and official labels for the OACs concomitant use of following drugs is not permitted during this observational study:

- With use of warfarin – allopurinol, ceftriaxone, derivatives of nitroimidazole (including metronidazole), imidazole group of antifungal, macrolides group With use of rivaroxaban and apixaban – HIV protease inhibitors, azole group of antifungal (in the case of systematic treatment).

With use of dabigatran – ketoconazole for systematic treatment, cyclosporine, itraconazole, tacrolimus, dronedarone.

Primary Outcome(s)

Proportion of highly and medium adherent patients according to 8-item Morisky Medication Adherence Scale

Secondary Outcome(s)

- Proportion of potentially adherent patients (answer “Yes” for question №5 of specifically designed 5-item questionnaire)
- Identification of baseline characteristics associated with adherence
- Correlation index between results of 8-item Morisky Medication Adherence Scale and specifically designed 5-item questionnaire
- Proportion of doctors prescribed OAC according guidelines.

Safety Outcomes

Adverse events and outcomes will be recorded from the start of treatment with the OAC until the end of the observational study period. The doctor will evaluate the severity of adverse events and outcomes if necessary takes measures for their medical treatment according to current clinical practice.

Information of every serious complication of drug treatment leading to patient’s hospitalization or development of life-threatening condition should be transmitted to the principal investigator in 24 hours since the information-receiving time.

Measurement of results (How assessed)

8-item Morisky Medication Adherence Scale will be used for evaluation of actual patient adherence to OACs (primary objective). Highly adherent patients will be identified with the score of 8 on the scale, medium adherers with a score of 6 to < 8, and low adherers with a score of <6. (Donald E. Morisky et al. J Clin Hypertens (Greenwich). 2008 May; 10(5): 348–354.)

8-item Morisky Medication Adherence Scale and specifically designed 5-item questionnaire will be used for assessment of potential and actual adherence to OACs. In virtue of results patients will be divide in groups: potential adherent, potential non-adherent, actual adherent to OAC with high, moderate and low level of adherence. Evaluation of correlation index between results of 8-item Morisky Medication Adherence Scale and specifically designed 5-item questionnaire will be

performed for validation of specifically designed 5-item questionnaire (only for actual adherence). 5-item questionnaire will be considered valid in the case of the level of the Kapp's consistency coefficient with the results of the Moriski-Green test more than 0.4.

Potentially adherent patients to OAC will be identified by answer “Yes” for question №5 of specifically designed 5-item questionnaire.

Identificated predictors for adequate adherence will be considered significant in case of p values < 0.05

Prescription OAC according to guidelines will be assessed “positive” if HCP follow next recommendations:

- 1) Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA2DS2-VASc score of 2 or more.
- 2) Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA2DS2-VASc score of 3 or more.
- 3) Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.
- 4) NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).
- 5) In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.

Visit schedule

Two visits at 6-month intervals are scheduled for each patient as part of routine clinical practice:

Visit 0– visit at study entry:

- receiving written informed consent to participate in research from patients
- inclusion in the program
- assessment of inclusion and exclusion criteria
- verification of non-valvular atrial fibrillation diagnosis (according to medical documentation, confirming the history of atrial fibrillation: ECG, Holter monitoring, etc..)
- collecting information on received medication therapy, including OACs
- physical examination of patients (measurements of blood pressure, heart rate, height, weight, waist circumference)
- questioning of patients to determine potential and actual adherence to OACs
- computation of points on the scale CHA2DS2-VASc and HAS-BLED to determine the indications for the appointment of the OACs and the identification of an increased risk of bleeding
- to determine the INR in patients who agreed to replace the use of warfarin to one of the NOACs

- prescription of OACs according to routine clinical practice and official labels for these medications
- instructing patients (according to the specifically designed scheme) to regularly take prescribed medications, be aware of precautionary measures when taking OACs, telling them about pros and cons of treatment with OACs

Visit 1 – visit at 6 months after the Visit 0:

- collecting information on patients' compliance with doctor's recommendations
- collecting information on patients' actual medication therapy
- collecting information on the safety of treatment with OACs (in case patient has been taking them), recording all adverse events that occurred during the study period
- measurements of blood pressure, heart rate as a part of routine clinical practice
- questioning of patients to determine potential and actual adherence to OACs

Follow-up period

Visit 2- follow-up calls to patients (one year)

Phone contact to determine patient's life status, possible endpoints (fatal and non-fatal thromboembolic complications of non-valvular atrial fibrillation) and fill (after receiving patient's consent) both questionnaires.

Statistical & Analytical Plan and Methodology

This study will include data on all patients present on the first visit to center (V0). An approximate number of patients to be included – 200.

1. Evaluation of actual adherence according to 8-item Morisky Medication Adherence Scale.
2. Determination of proportion of highly and medium adherent patients according to 8-item Morisky Medication Adherence Scale.
3. Evaluation of actual adherence according to 5-item questionnaire. Determination of proportion of highly and medium adherent patients according to 5-item questionnaire.
4. Evaluation of correlation index between results of 8-item Morisky Medication Adherence Scale and specifically designed 5-item questionnaire
5. Evaluate proportion of potentially adherent patients (which answered “yes” to the question #5 in the 5-item questioner).
6. Comparative analysis of actual adherence will be held according to both questionnaires (8 - and 5-item) in the following subgroups:
 - based on initial OAC therapy:
 - patients taking one of the NOACs
 - patients taking VKA

- patients taking no OACs

based on adherence according to data of specifically designed questionnaire:

1). adherent potentially

- non-adherent potentially

In the subgroups of patients receiving different NOACs (with various multiplicity of reception)

7. Detection of factors associated with adherence will be made using binary and multinomial logistic regression with determination of Odds ratio, 95% confident intervals and p values for each factor. Comparison on age, hemodynamic parameters (SYS, DIA, HR), BMI, sex, marriage status, educational level, employment, number of CVD risk factors, co-morbidity, number of medicine prescribed will be performed using Mann-Whitney U test for quantitative variable and chi-square and Z-test for categorical variable.

Significant factors of difference detected while analysis would be include into logistic regression models however model with satisfactory sensitivity and specificity might be difficult to develop due to small sample size which is difficult to enlarge.

8. Evaluate proportion of HCPs prescribed OAC according guidelines.

9. Missing data analysis will be made in the case of missing data in more than 5% of observations. Using the Roderick Little test results missing data will be either deleted (if $p > 0,05$, i.e. omissions are accidental) or restored by imputation (if $p < 0,05$ in the Roderick Little test).

Limitations

Criteria for selection of evaluable cases

This study will include data on all patients present on the Visit 0 to center.

Informational bias

8-item MMAS measured for actual adherence will be used to validate the measurement for potential adherence of 5-item questionnaire in this study. This can bring information bias.

Observer bias

Another potential limitation of the study design is that expectancies regarding study results can produce bias in the research outcomes.

Timelines

Planned Study Timelines:

Visit 0 - from 01.09.2017 to 01.12.2017

Visit 1 - from 01.03.2018 to 01.06.2018

Visit 2 (follow-up calls to patients) – from 01.03.2019 to 01.06.2019

Statistical analysis

Data from questionnaires and study cards of patients in the PROFILE registry will be analyzed using the statistical program IBM SPSS Statistic version 20 (IBM, USA) using descriptive statistics, parametric and nonparametric tests for quantitative and qualitative variables. Results of descriptive statistics will be presented with statistics mean and root-mean-square deviation for normally distributed random variables, with medians (25%, 75% quartiles) for non-normally distributed random variables, with a percentage for quantitative variables.

Student's t-test will be used for comparative analysis of groups with different levels of medication adherence (high, medium, low according to the 8-item Morisky Medication Adherence Scale, potential and actual – according to specifically designed questionnaire). The validation of ‘potential adherence’ will be assessed using sensitivity/(1-specificity) measure by using the validated Morisky scale, where sensitivity measures the proportion of positives that are correctly identified and specificity measures the proportion of negatives that are correctly identified. Mann-Whitney U test (for qualitative variables), χ^2 test (for categorical variables), Fisher's exact test (for contingency tables 2x2), z-test (for comparison of proportions), binary and multinomial logistic regression to determine factors associated with adherence to NOACs (with determination of odds ratio, 95% confident intervals and p values for each factor and combination of factors) will be used.

p values <0.05 will be considered significant. Kappa coefficient will be used for validation of specifically designed 5-item questionnaire (only actual adherence). Kappa coefficient values exceeding

0.75 indicate a high consistency of assessments. Values ranging from 0.4 to 0.75 indicate good to noticeable degree of coherence. Values below 0.4 mean a weak degree of consistency of estimates.

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