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Analysis of latest international studies for atrial fibrillation: trends and perspectives

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Summary

The urgency of atrial fibrillation (AF) as the health and social problems, primarily due to the fact that the rhythm of the heart, being a significant cause of heart failure, stroke and other thromboembolic complications, significantly increases the relative risk of total and cardiovascular mortality. In addition, complications of AF are the cause of persistent disability of working age. All this leads to the continuation of a number of randomized studies examining the effectiveness of various methods to control the heart rhythm and heart rate, as well as improving the prognosis of the disease. In this article the provisions concerning drug and non-drug treatment of diseases, subject to revision in the latest national and international guidelines.

Keywords

Atrial fibrillation, recommendations, anticoagulants, antiarrhythmic drugs, ablation

Atrial fibrillation: importance, prevalence, prognosis

Atrial fibrillation (AF) is the most common supraventricular arrhythmia. It is characterized by irregular excitation and contraction of different myocardial parts with heart rate up to 400-700 beats per minute without regular contraction [1]. In Russia both terms, AF and ciliary arrhythmia, the one that has been proposed by G. F. Lang, are equally common to use.

The problem of AF is very important because this arrhythmia, being one of the causes of heart failure, stroke and other thromboembolic complications, significantly increases relative risk of total and cardiovascular mortality. Although AF has high occur-

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rence and relatively benignant course nowadays this arrhythmia is considered to be life-threatening because of big number of consequences that not only reduce quality of life but also increase frequency of severe complications and death. It is known that AF increases five-fold the risk of brain stroke. Frequently ischemic stroke in patients with AF is recurrent and results in the death of patient increasing the costs of treatment [2].

As we mentioned before, AF is one of the most common arrhythmias, occurs in 1–2% of population, and the frequency of AF increases with age. Multicentral trials revealed that the prevalence of this pathology in patients younger than 60 years is ~ 0,5%, in patients over the age of 60 years – 5%, over the age of 75 years – more than 10%. It has been shown that men are more likely to develop AF than women. AF paroxysm is the reason of more than ⅓ of patients' admissions to hospital with arrhythmia [3]. Because of extended lifespan the prevalence of AF has increased by 13% during last 20 years. According with prognosis this number would double during next 50 years. According with AHA (American Heart Association) from 2.7 to 6.1 mln of adult Americans suffer from AF and this number would double during next 25 years. Previously valvular defects (mitral stenosis) were considered to be the most frequent cause of AF. Nowadays arterial hypertension is supposed to be the main etiological agent of AF and the number of patients with idiopathic AF is increasing [4].

Prognosis for patients with AF depends on hemodynamic and thrombogenic complications of this arrhythmia at first, but it is also linked with patient's age, presence and severity of concomitant diseases. AF can be life-threatening because of the risk of thromboembolic complications and myocardial dysfunction that can promote development of heart failure.

Results of REACH trial that involved more than 63 000 patients suffering from AF demonstrated significantly higher frequency of cardiovascular death, myocardial infarction (MI), stroke and higher need of hospital admission comparing with patients without AF [5]. It is known that ~ ⅓ of all strokes is associated with AF. Stroke frequency in patients with nonvalvular AF taking anticoagulants is 5% per year, it is 2–7 times higher than stroke frequency in patients without AF. Cerebrovascular complication of AF are particularly frequent in elderly patients. According with Fremingham study for patients with AF (recruiting n=5070 patients during 34 years) the risk of stroke in the age of 50–59 years increases by 4 times, in the age of 60–69 years – by 2.6 times, 70-79 years – by 3.3 times, 80–89 years – 4.5 times. Mitral valvular disease, first of all mitral valve stenosis, is an important risk factor of stroke development. In case of nonvalvular AF such factors like previous episodes of embolism and strokes, arterial hypertension, age >65 years, information about MI, diabetes mellitus in anamnesis, prominent systolic dysfunction and/or congestive heart failure, enlarged left atrium (>50 mm), the presence of thrombus in left atrium can promote developing of stroke [6].

AF can play a role of both initial and aggravating agent for heart failure. Patients with AF have 3-4 times higher risk to develop heart failure. Increased heart rate in AF causes hemodynamic disorders due to reduced filling of ventricles, impaired coronary blood flow and heart contractility, and dilatation of ventricles. If heart rate >130 beats per minute persists for 10-15% of the entire daytime it can lead to developing of tachycardia-induced cardiomyopathy with severe congestive heart failure. But even if heart rate is normal lack of adequate atrial influence on cardiac output and irregular heart rhythm considerably aggravate hemodynamics. In this case stroke volume reduces by 20%, cardiac output – by 0.8–1.0 l/min and pulmonary artery wedge pressure – by 3–4 mm Hg.

Concomitant diseases of cardiovascular diseases has a big impact on prognosis of patients with AF. Patient with arterial hypertension and AF has twofold higher risk of developing complications during 5 tears, five-fold increase in frequency of left ventricle failure developing, three-fold increase in stroke development frequency and three-fold increase of mortality frequency. In case of MI lethality is twice higher and mortality is 1.8 times higher. According with different studies, presence of AF in patients with heart failure gives 2.7–3.4-fold increase in mortality rate and doubles ther risk to develop stroke and thromboembolic complications [7].

Key points of European and Russian guidelines for treatment and prevention of complications

Last Guidelines of European Society of Cardiology (ESC) dedicated to treatment of patients with AF were published in 2012. National Guidelines for diagnostics and treatment of AF proposed by Russian Society of Cardiology (RSC), National Scientific Community of arrhythmologists and Russian cardiovascular sur-

geons association also were revised and published in 2012. It is worth to mention that last National Guideline contains all available information related to this problem including united guidelines of American Heart Association, American College of Cardiology and guidelines of ESC.

Some essential changes in strategies of rhythm and heart rate control and in prevention of stroke and thromboembolic complications have happened after release of previous edition of guideline in 2011. Published results of 3 major studies changed some positions of these guidelines. These trials are: ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in AF), ROCKET-AF (Rivaroxaban Once-daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in AF) and PALLAS (The Permanent AF Outcome Study Using Dronedarone on Top of Standard Therapy) [8, 9]. First two clinical trials were dedicated to new anticoagulants: rivaroxaban and apixaban, therapeutic indications for which had been considerably extended.

The PALLAS study recruited 3236 patients but it had been terminated ahead of schedule due to increase of frequency of reaching the first endpoint (stroke) from 1.2% in placebo group to 2.6% in patients taking dronedarone (Hazard ratio (HR) 2.29, p=0.02) and also because of increased MI rate: from 4.1% in placebo group comparing with 7.8% in patients receiving dronedarone (HR 1.97, p=0.001). At the same time statistically significant increase of HR for compromised liver function during dronedarone treatment comparing to placebo had been detected: it occurred in 3.8% and 1.7% of patients consequently (p<0,001) [10].

According with epidemiological characteristic of AF in both guidelines, prevalence of AF in general population is up to 2%. And AH is considered to be the main cause of AF development. ESC highlights the importance of active case finding of AF in stroke prevention. This statement is based on several studies demonstrating that even short episodes and so-called "latent" AF increase the risk of stroke development. Therefore for opportune diagnostics of arrhythmia in patients older than 65 years it is necessary to perform screening including pulse palpation and ECG.

In AF classification apart of categories that have been used for a long time in clinical practice: first detected, paroxysmal, persistent, permanent, it is recommended to define also longstanding persistent AF. This arrhythmia is diagnosed when AF persists for more than one year and the strategy of sinus rhythm restoration has been chosen [2].

For quantitative estimation of AF symptoms it is recommended to use EHRA (European heart rhythm association) score. This score considers 4 classes of symptoms. This scale has been created relatively recently and it allows to estimate the symptoms associated with arrhythmia and their dynamics after sinus rhythm restoration [11].

Strategic attempt to save sinus rhythm has no advantages over "non-intervention" approach to the natural course of arrhythmia provided that the heart rate is under control. This position remains unchanged. At the same time it is proved that excessive heart rate control doesn't improve patients' prognosis. Talking about therapy of AF it is worth to mention that this section of ESC guideline has to be adapted to Russian clinical practice. In ESC guideline ideas about some antiarrhythmic drugs are based on major international clinical trials. At the same time in Russia and some other ex-soviet countries some drugs like allapinin, etacizin, procainamide produced in these countries are successfully used in clinical practice.

Section of antiplatelet therapy of patients with AF makes emphasis on so-called "new oral anticoagulants" (NOAC): direct thrombin inhibitors and direct Xa factor inhibitors. NOAC can be considered as an alternative of vitamine K antagonists. NOAC have some advantages over them like predictable anticoagulant effect with no necessity of constant coagulogram control, less prominent interaction with drugs and food, better efficacy-safety ratio. Key ideas about acetylsalicylic acid (ASA) has been proposed. It is highlighted that preventive efficacy of ASA is not high and the risk of massive bleedings still persists especially in elderly patients. Combined therapy of ASA and clopidgrel should be restricted to small group of patients that refuse to take NOAC.

Naturally risk stratification in patients with AF in relation to thromboembolic complications and stroke in particular remains an important problem. For a long time CHADS2 (Congestive Heart failure, Hypertension, Age, Diabetes mellitus, Stroke (2 ball)) has been used for this purpose.

Last guideline proposes more comprehensive score CHA2DS2-VASc (Congestive Heart failure, Hypertension, Age (2 points), Diabetes mellitus, Stroke (2 points), Vascular disease, Age, Sex category). It gives one point for presence of heart failure, AH, diabetes mellitus, vascular disorders: history of

MI, atherosclerosis of lower extremities vessels and aorta, age of 65–74 years and female sex. This score gives 2 points for age more than 75 years and prior episodes of stroke, transitory ischemic attacks or thromboembolism. CHA2DS2-VASc score for non-valvular AF has wider range of points, includes more risk factors: female xex, age of 64-75 years and vascular disorders. for example women cannot get the score of 0 points according with CHA2DS2-VASc. It is commonly known that CHA2DS2-VASc allows to estimate the risk of stroke development in more detailed and precise way especially in patients with low risk [2].

ESC and RSC guidelines give more importance to radiofrequency ablation (RFA) also as an initial treatment of AF with prominent symptoms and severe clinical course. It is reasonable to perform catheter ablation before prescribing antiarrhytmic drugs in patients with recurrent paroxysmal AF associated with symptoms of hemodynamic disorders after comparing benefits and risks.

New trends in AF treatment: clinical studies results

Majority of AF relapses after pulmonary veins isolation are caused by restoration of conduction between them and left atrium. The UNDER-ATP (UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate) [12] study estimated possibility of reducing relapse risk by additional use of RFA during the first ablation procedure in the areas of conduction induced with ATP (adenosine triphosphate). After randomization 2113 patients with paroxysmal, persistent or longstanding persistent AF underwent pulmonary veins isolation with ATP administration (n=1112) or according with standard protocol (n=1001). Mentioned below conditions have been chosen as a primary endpoint: relapse of atrial tachycardia lasting more than 30 sec or requiring repeated ablation, hospitalization or administration of I and III class of antiarrhythmic drugs during the period since 90 days up to one year after ablation. In the group of patients who underwent pulmonary veins isolation with ATP administration (0.4 mg/kg) conduction between pulmonary veins and left atrium was induced in 307 (27.6%) patients but it was eliminated with additional procedure of RFA in 302 (98.4%) patients. During the first year primary endpoint events haven't been registered with the same frequency in both groups: 68.7% in the group of pulmonary veins isolation with ATP administration and 61.7% in the group of patients who underwent pulmonary isolation according with standard protocol (corrected HR 0.89, for confidence interval (CI) 95% from 0.74 to 1.09 (p=0.25)).

Majority of early AF relapses after ablation are caused by postoperative vulnerability of left atrium. The EAST-AF study (Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for AF trial) [13] investigated capability of antiarrhythmic drugs administered during first 90 days after ablation to reduce the risk of early AF relapse, to decrease left atrium remodeling and to improve long-term clinical outcome. After catheter RFA 2038 patients with paroxysmal, persistent or longstanding persistent AF were randomized for 90 days of I and III class antiarrhytmic drugs administration or for refusal of treatment (n=1022). Primary endpoint events included atrial tachycardia lasting more than 30 sec, necessity of repeated ablation, hospitalization or administration of I and III class of antiarrhythmic drugs during the period since 90 days up to one year after ablation. During first 90 days after ablation absence of relapses have been registered with higher frequency in the group of antyarrhytmic pharmacotherapy: 59.0% versus 52.1% in control group, HR 0.84 for 95% CI from 0.73 to 0.96 (p=0.01) but during the period of further follow-up observation the absence of primary endpoint events in both groups had no significant differences: 69.5% and 67.8% respectively, corrected HR 0.93 for 95% CI from 0.79 to 1.09 (p=0.38). Administration of antiarrhytmic drugs during 90 days after AF ablation decreases the frequency of atrial tachiarrhytmia in this period of treatment but doesn't improve clinical outcome during subsequent follow-up observation.

In case of long-standing persistent AF pulmonary veins isolation is not enough for achievement of successful ablation. In the BELIEF study (Effect of Empirical Left Atrial Appendage Isolation on Long-term Procedure Outcome in Patients With Persistent or Long-standing Persistent AF Undergoing Catheter Ablation) [14] 173 patients with long-standing persistent AF after randomization underwent standard procedure of pulmonary veins isolation (n=88) or standard procedure together with electric isolation of left atrial auricle with average duration of procedure 77 versus 93 min, respectively.

Patients who underwent electric isolation of left atrial auricle had no AF relapses during one year of observation: 56% versus 28% in control group, HR 1.92 (p=0.001). Both groups of patients then underwent repeated ablation with isolation of left atrial auricle. During 2 years of observation AF haven't been

registered in 76% of initially performed left atrial auricle isolation and in 56% of patients who underwent it during the second procedure (p=0.003). Left atrial auricle isolation seems to be reasonable and requires pathophysiological investigation.

Comparing with vitamin K antagonists NOAC have short half-life time that requires high patients' compliance. Randomized trial AEGEAN (Assessment of an Education and Guidance program for Eliquis Adherence in Non-valvular AF) [15] involved patients with AF taking apixaban either being involved into educational program: information leaflet, special key holder, mobile phone notification, access to virtual coagulologic clinic(n=579) or receiving information about the disease and its treatment in standard way. Adherence to apixaban treatment regimen (twice for a day) was controlled using electronic gadget inside the box of the medicine. During 24 weeks patients took anticoagulant daily and on regular basis in 88,3% and 88,5% of cases (p=0.89), didn't interrupt the treatment on the 30th day of treatment in 91.1% and 90.5% of cases (p=0.76) in the groups of educational program and control, respectively. This study didn't find out additional benefit of educational program in patients with AF during treatment with apixaban.

During standard electric cardiostimulation such problems like electrode displacement and failure, infection, heart perforation, vein occlusion, tricuspid regurgitation, can occur. In the LEADLESS II study [16] totally leadless autonomous cardiac stimulators (42 mm long, 6mm diameter) were implanted in non-surgical way (catheter, via femoral artery) into the right ventricle of 300 patients who needed constant one-chamber stimulation Acceptable threshold ≤ 2,0 V with duration 0.4 mc and stimulation amplitude after 6 month was chosen as a primary efficacy endpoint and absence of serious adverse effects related to stimulator after 6 months was taken as a primary safety endpoint. Primary efficacy and safety endpoints were achieved in 90% and 93.3% of patients, respectively. During 6 month electrode displacement occurred in 1.7% of patients, heart perforation – in 1.3% of cases and ineffective stimulation – in 1.3% of cases. Later cardiostimulator was implanted to 226 patients and complications rate had a tendency to decrease. Working period of battery is estimated as 15 years. The question about tactics in case of cardiostimulator failure (remove or implant another one) hasn't beens solved yet.

Conclusion

Increasing prevalence of AF and its complications requires further investigation of efficiency of different approaches for heart rhythm control and rate of ventricular contractions and also antiplatelet drugs efficiency in this category of patients. Results of clinical studies presented at the last meeting of ESC that took place in London in autumn of 2015 certainly will be used in new guidelines for treatment of patients with AF.

Conflict of interest: None declared.

References

1. Kushakowski MS, Grishin YN. Cardiac arrhythmias. M.: Foliant; 2014, 720 p. Russian.
2. National guidelines for diagnosis and treatment of atrial fibrillation. RSC, RSSC and CSA. Moscow: 2012, 100 p. Russian.
3. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC guidelines for the management of atrial fibrillation. Eur Heart J. 2012; 33:2719-47.
4. AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. JACC. 2014;64(21):2246-80.
5. Cacoub PP, Abola MT, Baumgartner I., et al. Cardiovascular risk factor control and outcomes in peripheral artery disease patients in the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Atherosclerosis. 2009;204(2):86-92.
6. Oganov RG, Salimov VA, Bokeria LA, et al. Clinical guidelines for diagnosis and treatment of patients with atrial fibrillation. Bulletin arrhythmology. 2010; 59: 53-77. Russian.
7. Sychev O. Atrial fibrillation. Modern approaches to the treatment and prevention of complications in patients with concomitant heart disease. Ukrain. Med. J. 2011; 10-12: 54-8. Russian.
8. Granger CB, Alexander JH, McMurray JJ, et al., for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011; 365: 981-92.
9. Patel MR, Mahaffey KW, Garg J, et al., for the ROCKET-AF Investigators. Rivaroxaban versus warfarin in nonvalvularatrial fibrillation. N Engl J Med 2011; 365: 883-91.
10. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med. 2011; 365:2268-76.
11. Kirchhof P, Auricchio A, Bax J, et al. Outcome parameters for trials in atrial fibrillation: executive summary. Recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork (AFNET) and the European Heart Rhythm Association (EHRA). Eur Heart J. 2007;28: 2803-17.

12. Kazuaki K, Koichi I, Atsushi K, et al. Slides of the Summary Presentation of the "UNmasking Dormant Electrical Reconduction by Adenosine TriPhosphate" presented on 30th August 2015 at Hotline Session at the European Society of Cardiology Congress 2015, aviable from: http://www.escardio.org
13. Atsushi K, Koichi I, Kazuaki K, et al. Slides of the Summary Presentation of the " Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for Atrial Fibrillation trial" presented on 30th August 2015 at Hotline Session at the European Society of Cardiology Congress 2015, aviable from: http://www.escardio.org
14. Luigi Di Biase. Slides of the Summary Presentation of the "Effect of Empirical Left Atrial Appendage Isolation on long-term procedure outcome in patients with Long-Standing Persistent AF undergoing Catheter Ablation: Results from the BELIEF Randomized Trial" presented on 30th August 2015 at Hotline Session at the European Society of Cardiology Congress 2015, aviable from: http://www.escardio.org
15. Montalescot G, Brotonos C, Cosyns B, et al. Slides of the Summary Presentation of the "Assessment of an education and guidance program for apixaban adherence in non-valvular atrial fibrillation: the randomised AEGEAN study" presented on 30th August 2015 at Hotline Session at the European Society of Cardiology Congress 2015, aviable from: http://www.escardio.org
16. Reddy VY, Bunch TJ, Cantillon DJ, et al. Slides of the Summary Presentation of the "Safety and Efficacy of a Leadless Pacemaker: Results from the LEADLESS II clinical trial" presented on 30th August 2015 at Hotline Session at the European Society of Cardiology Congress 2015.