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Patient-centered management of atrial fibrillation: from guidelines to clinical practice

Kanorskiy S. G., Polishchuk L. V.

Kuban State Medical University, Krasnodar, Russia

Authors

Sergey G. Kanorskiy*, M.D., PhD., Doctor of Sciences, professor, Head of the Internal Medicine Department № 2, Kuban State Medical University, Krasnodar, Russia.

Lily V. Polishchuk, M.D., PhD Student, Internal Medicine Department № 2, Kuban State Medical University, Krasnodar, Russia.

Abstract

The current article discusses the updated European Society of Cardiology (ESC) Guidelines on diagnosis and treatment of atrial fibrillation and their application in daily patient-centered clinical practice that emphasizes rate and rhythm control.

Keywords: *atrial fibrillation, rate control, rhythm control.*

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The estimated prevalence of atrial fibrillation (AF) is around 2–4 % [1], which makes it the most common stable arrythmia in adult population. The number of patients with AF is expected to rise partly due to the better diagnosis of asymptomatic forms, longer life expectancy and to the development of diseases that increase the risk of AF [2, 3, 4]. It was previously estimated that AF developed in 1 in 4 people over 55 years, and now the estimated risk in the European population is 1 in 3 people [5]. AF is associated with increased mortality, stroke, heart failure (HF), cognitive decline, vascular dementia, depression, decreased quality of life, increased number of hospitalizations and therefore is a great burden for patients, physicians and healthcare system worldwide. Large resources are required annually for research related to new and ef-

* Corresponding author. E-mail: kanorskysg@mail.ru

fective AF prevention and treatment approaches, its mechanisms and predictors. New scientific data is constantly generated and evaluated in order to create new evidence-based clinical guidelines. On the August 29th 2020 the European Society of Cardiology (ESC) presented the updated guidelines for the diagnosis and management of AF developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). The guidelines emphasize the need of multifaceted and multidisciplinary approach to AF management that requires active patient collaboration with the physicians. The "Atrial Fibrillation Better Care — ABC" pathway that was proposed in the guidelines aims to further improve the management of AF patients concentrating on their interests and improving the treatment outcomes [6].

The current article discusses the updated 2020 ESC guidelines on diagnosis and treatment of atrial fibrillation and their application in daily patient-centered clinical practice that emphasizes rate and rhythm control.

Diagnosis and structured characteristics of atrial fibrillation

Atrial fibrillation diagnostic approach was extended with a requirement to document an electrocardiogram (ECG) finding in patients with diagnosed AF. A 12-lead ECG or a single-lead ECG tracing of≥30 s showing heart rhythm with no discernible repeating P waves is required for diagnosis of AF, which is the 2007 consensus of Heart Rhythm Society (HRS), European Heart Rate Association (EHRA) and European Cardiac Arrhythmia Society (ECAS) (Class I) [7]. This is the first step of the proposed "CC to ABC" pathway, according to which the first step is to confirm the presence of AF. Then, AF is characterized, which includes the assessment of stroke risk, symptom severity, severity of AF burden and substrate severity in all patients with AF. Such a structured characterization simplifies clinical evaluation of patients with AF and helps to make right decisions concerning the optimal clinical management (Class IIa). The 4 characteristics that were mentioned previously make up the "4S-AF" (("Stroke risk", "Symptom severity", "Severity of AF burden", "Substrate severity") [8]. The existing tools used for risk assessment are currently integrated into a scheme, but as new technologies are constantly emerging the best instruments will be determined later. Severity of AF burden (Sb) means the AF clinical form (paroxysmal, persistent, longstanding persistent, permanent). Substrate severity (Su) is associated with the AF pathophysiology severity and includes both the simple clinical patient characteristics (age, cardiovascular risk factors) and the comorbidities, the presence and extent of left atrial distention, atrial malfunction and atrial myocardial fibrosis. Transthoracic echocardiography is widely available in everyday clinical practice and provides the main information about atrial size and function. More complicated methods include transesophageal echocardiography, computed tomography or magnetic resonance imaging and allow to evaluate the additional parameters and structural changes of the atria including the level of fibrosis and the presence of epicardial adipose tissue. These parameters can be used as prognostic values and taken into consideration when making the decision about, for instance, the optimal ablation strategy.

Integrated management of patients with atrial fibrillation

Integrated management of AF patients requires a coordinated and agreed patient-individualized care pathway to deliver optimized treatment by an interdisciplinary team. In the 2020 document the class of the recommendations that promote patient-centered approach was increased. Treatment options should be discussed with the patient, and the patient should also be informed about the pros/cons and risks/benefits of certain options and the management plan should be agreed in discussion with the patient and healthcare professionals (Class I). Regular collection of "PRO" ("patient-reported outcomes") is recommended for evaluation of treatment effects and improvement of patient care (Class I). International Atrial Fibrillation Patients and Healthcare Workers Consortium selected the following important PRO: health-related quality of life, physical and emotional functioning, cognitive functions, symptom severity, exercise tolerance and working capacity. Incorporation of PRO in the process of AF treatment is discussed in the special document developed by the EHRA in collaboration with patients' representatives [9].

"ABC" pathway in treatment of atrial fibrillation

"ABC" pathway was developed to make the integrated AF patient care more effective on all levels of healthcare and in all providers. It includes three most crucial aspects of atrial fibrillation treatment: "A" — Anticoagulation/Avoid stroke, "B" — Better symptom

management, "C" — Cardiovascular and Comorbidity optimization.

Anticoagulation and stroke avoidance

This crucial aspect of atrial fibrillation treatment was expanded with several new points. In order to officially assess bleeding risk in patients with AF taking oral anticoagulants it is necessary to calculate HAS-BLED score. That can help eliminate the modifiable bleeding risk factors and reveal the patients at a very high risk of bleeding (HAS-BLED score≥3) who require earlier and more frequent follow-up (Class II). The decision on starting anticoagulation therapy in patients with atrial fibrillation shouldn't be based on the calculated risk of bleeding alone in the absence of absolute contraindications to oral anticoagulation for stroke prevention. Regular stroke and bleeding risk reassessment is recommended for optimal management decisions (e.g. starting oral anticoagulation in patients who don't have low stroke risk anymore) and elimination of modifiable bleeding risk factors (Class I). In patients with AF who had low stroke risk at the first place, the first reassessment should be performed in 4–6 months (Class IIa). For patients taking warfarin in whom the INR (International Normalized Ration) was in the therapeutic range less then 70 % of time (time in therapeutic range (TTR)<70 %) the following options are recommended: switching to oral anticoagulants that are not vitamin K antagonists (for patients without mechanical valves or with moderate or severe mitral stenosis but with good adherence to treatment (Class I)) or efforts to improve TTR (e.g. education/counselling and more frequent INR checks) (Class IIa).

Better symptom control

Rate control

In the 2020 ESC Guidelines the current approach stayed unchanged: rate control is still considered to be sufficient to improve AF-related symptoms. Clinical studies didn't produce any evidence of the best type and intensity of rate control [10–12]. The optimal heart rate target range in patients with AF is still unknown. Of all the studies on this topic, the randomized controlled RACE (Race Control Efficacy in Permanent Atrial Fibrillation) II trial is still the key one. In the RACE II trial there was no difference in clinical events, Ney York Heart Association (NYHA) class or hospitalizations between the strict [target heart rate<80 beats per minute. (bpm) at rest and<110 bpm during moderate exercise] and mild (<110 bpm at rest) heart rate control [13, 14]. Similar results were reported earlier in the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) и RACE trials [15]. Therefore, in accordance with the results of these studies, mild heart rate control (<110 bpm according to a standard 12-lead ECG) is an acceptable initial approach (Class IIa, level B) regardless of HF status (with the exception of tachycardia-induced cardiomyopathy), unless symptoms require stricter rate control.

According to our studies [16, 17], in the patient-centered approach the optimal heart rate target range can be selected with the intention to balance cardioprotection and sufficient peripheral hemodynamics in order to avoid local, primarily cerebral, prothrombotic state. In one randomized prospective study we assessed the levels of high-sensitivity cardiac troponin I (cTnI-hs), mean blood flow velocity and the pulsality index using the high-frequency power doppler ultrasound with fluorescence in 150 patients with stable AF aged 74±8 years, randomized into 2 groups depending on the target heart rate range at rest: 60–79 bpm (first group, n=75) and 80–100 bpm (second group, n=75). Patients who completed the study protocol were included into the analysis. The level of cTnI-hs was significantly reduced in both treatment groups, but the reduction was more profound in the 60–79 bpm group — 2.1 (1.6; 3.9) ng/L — median (25^{th} percentile; 75^{th} percentile) versus 1.1 (0.7; 2.4) ng/L in the second group ($p<0.001$) that represents the reduction in the chronic myocardial damage. Spearman's correlation coefficients between the levels of heart rate reduction and cTnI-hs concentration were 0.45 ($p<0.001$) and 0.44 ($p<0.001$) in the first and second groups respectively. Mean blood flow velocity increase and the pulsality index reduction was noted in both groups but was more profound in the second treatment group (80–100 bpm) that signified the better tissue perfusion. Therefore, the level of chronic myocardial damage that is assessed by the cTnI-hs levels, and the tissue perfusion markers can become the basic values for heart rate target range determination in the patient-centered AF treatment approach.

In the 2020 ESC guidelines beta-adrenoblockers or non-dihydropyridine calcium channel blockers (CCBs) are recommended as the first-line agents for heart rate control in patients with AF and left ventricular ejection fraction (LVEF)≥40 % (Class I). This recommendation is based on the results of the Ulimoen SR, et al. (2013) [18], Scheuermeyer FX, et al. (2013) [19],

Tisdale JE, et al. (1998) [20] and Farshi R, et al. (1999) [21] studies. Digoxin is still considered to be the second-line agent in this patient cohort. In patients with AF and LVEF<40 % beta-blockers and/or digoxin are still recommended for heart rate control (Class I) according to the Nikolaidou T, et al. (2009) [22], Kotecha D, et al. (2014) [23], Ziff OJ, et al. (2015) [24], Darby AE, et al. (2012) [25], Khand AU, et al. (2003) [26], Lewis RV, Irvine N & McDevitt DG (1988) [27] and Mulder BA, et al. (2014) [28] studies. Currently a major randomized trial DIGIT-HF (DIGitoxin to Improve ouTcomes in patients with advanced chronic Heart Failure) that studies digoxin in chronic CHF patients is in progress [29].

Rhythm control

According to the 2020 ESC guidelines, the main indication for the sinus rhythm control in patients with AF is the improvement of AF-related symptoms and quality of life in symptomatic patients. These beneficial effects were demonstrated in the leading randomized controlled trials. The results of EAST-AFNET 4 (Early treatment of Atrial fibrillation for Stoke prevention Trial) [30, 31] trial that evaluated the effects of early sinus rhythm control on the clinical outcomes in patients with newly diagnosed AF were presented on the ESC 2020 Congress and are further discussed in the current article.

An attempt to restore the sinus rhythm can also be performed for evaluation of treatment response in patients without clear connection between symptoms and the presence of AF. Rhythm control is preferred in the presence of the following factors: young age; first AF episode of short AF history; tachycardiomyopathy; normal or moderately increased left atrial volume; normal or moderately decreased atrial conduction (the signs of left atrial remodeliing); absence or a low number of comorbidities; difficulties with rate control; AF precipitated by a temporary event (e.g. acute disease); patient's preference.

Pharmacological cardioversion is indicated only in hemodynamically stable patients and the pulmonary emboly risk should be taken into consideration (Class I). Pharmacological cardioversion shouldn't be performed in patients with sick sinus syndrome, reduced atrioventricular conduction or QT prolongation (>500 ms) until the risks of proarrhythmic effects and bradycardia are considered (Class III). It is recommended to emphasize the importance of the treatment adherence and the need of oral anticoagulation both before and after cardioversion (Class I). In patients with AF>24 hours who undergo cardioversion therapeutic anticoagulation should be continued for at least 4 weeks even after successful cardioversion with sinus rhythm restoration (after 4 weeks the decision about the anticoagulation continuation should be made based on the stroke risk factors) (Class IIa). Patients with AF⩽24 hours who are at a very low risk of stroke (CHA2DS2-VASc 0 points in men or 1 points in women) anticoagulation in the 4 weeks after cardioversion can be neglected (Class IIb).

In the long-term AAD rhythm control the following aspects are important: AAD is only moderately effective for maintaining sinus rhythm; effective antiarrhythmic therapy only recuses but doesn't eliminate fibrillation relapses; proarrhythmic and other adverse events are often seen and the choice of AAD therapy should be based primarily on the safety profile. Sotalol can be considered for the long-term rhythm control in patients with normal LV function or with coronary artery disease with the control of QT interval, plasma potassium concentration, creatinine clearance and other proarrhythmic risk factors (Class IIb). The recommendation to use amiodarone for rhythm control in patients with AF (also in patients with HFrEF) was improved to Class I, but other AAD should be considered when feasible because of the extracardiac toxicity of amiodarone.

In the 2020 ESC guidelines catheter ablation (CA) still remains the treatment option for symptomatic AF except for patients with high risk of tachycardia-induced cardiomyopathy when this procedure is recommended for LV function correction (Class was increased to I) independently from the presence of symptoms. AATAC (Ablation vs Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device) and CASTLE-AF (Catheter Ablation vs Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation) [32, 33] as well as the CABANA (Catheter ABlation vs ANtiarrhythmic Drug Therapy for Atrial Fibrillation) [34] trials showed that CA had some effects on the morality and hospitalization frequency in patients with AF and HFrEF. Therefore, the 2020 ESC guidelines note that CA should be considered in certain patients with HFrEF and AF for survival benefits and the reduction of hospitalizations (Class IIa). CASTLE-AF and CABANA [35] studies are known to have certain limitations and AMICA (Atrial Fibrillation Management in Congestive Heart Failure With Ablation) [36] trial hasn't shown CA to improve LVEF in patients with LVEF⩽35 %. compared to pharmacological therapy.

For the decision on AF catheter ablation, it is recommended to take into consideration the procedural risks and the major risk factors for AF recurrence following the procedure and discuss them with the patient (Class I). AF catheter ablation means ablation for pulmonary veins isolation (PVI). According to the CAPTAF (Catheter Ablation compared with Pharmacological Therapy for Atrial Fibrillation) [37] trial results, the guidelines now state that AF catheter ablation for PVI should be considered for rhythm control after one failed or intolerant to beta-blocker treatment to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF (Class IIa) or persistent AF without major risk factors for AF recurrence as an alternative to AAD class I or III, considering patient choice, benefit, and risk (Class IIb). Catheter ablation after unsuccessful treatment with AAD class I or III to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF (Class I). Each if these approaches emphasize the central role of the patient. Catheter ablation in patients taking oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban or edoxaban) is recommended without OAC interruption. Risk factors for atrial fibrillation relapse after ablation include: left atrial size, AF duration, age, kidney dysfunction, substrate severity according to the MRI. All scales that estimated the risk of AF relapse showed the same effectiveness [38]. Repeated PVI procedures should be considered in patients with AF recurrence provided the patient's symptoms were improved after the initial PVI (Class IIa). Strict control of risk factors and avoidance of triggers are recommended as part of rhythm control strategy Class I). This new recommendation was added in the 2020 guidelines because the effects of strict RF control and trigger avoidance have been shown to affect CA outcomes. Effective treatment of arterial hypertension, diagnosis and treatment of obstructive sleep apnea, reduction of excessive alcohol consumption, hyperlipidemia control, smoking cessation, BMI reduction if the patient is overweight or obese (<27 kg/m^2) and hyperglycemia control.

Cardiovascular risk management and concomitant diseases treatment in patients with AF

Cardiovascular risk management and treatment of concomitant chronic diseases are crucial in patients with AF (Class I). Modification of unhealthy lifestyle and targeted therapy of intercurrent conditions is recommended to reduce AF burden and symptom severity. Opportunistic screening for AF is now recommended in patients with arterial hypertension (Class I) and obstructive sleep apnea (Class IIa). Recommendation class of exercise was decreased to Class IIa. Physical activity should be promoted in patients with AF in order to decrease the risk of relapse. Excessive exercise should be avoided as they can precipitate AF. Recommendation class of obstructive sleep apnea treatment was also decreased to IIb. Optimal treatment of OSA can be considered for the reduction of AF prevalence, progression and relapse frequency as well as symptom severity.

Specific clinical states

New recommendations were presented for patients with AF and acute or chronic coronary syndromes and for those who undergo percutaneous coronary intervention (PCI). In AF patients with ACS undergoing an uncomplicated PCI, early cessation (<_1 week) of aspirin and continuation of dual therapy with an OAC and a P2Y12 inhibitor (preferably clopidogrel) for up to 12 months is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespectively of the type of stent used (Class I). After uncomplicated PCI, early cessation (<_1 week) of aspirin and continuation of dual therapy with OAC for up to 6 months and clopidogrel is recommended if the risk of stent thrombosis is low or if concerns about bleeding risk prevail over concerns about risk of stent thrombosis, irrespectively of the type of stent used (Class I).

EAST-AFNET 4 study

The EAST-AFNET 4 project results were presented on August 29, 2020 simultaneously with the new 2020 ESC guidelines and therefore couldn't be taken into consideration when the guidelines were developed. The results of this study can influence treatment choices. In this international, investigator-initiated, parallel-group, open, blinded-outcome-assessment trial, 2789 patients who had early atrial fibrillation (diagnosed≤1 year before enrollment) and cardiovascular conditions were randomized to receive either early rhythm control or usual care [30]. Early rhythm control included treatment with AAD (flecainide, amiodarone, dronedarone, propafenone) or catheter ablation after randomization. Usual care included the management of AF–related symptoms. Two primary endpoints were determined: the first primary endpoint was a composite of death from cardiovascular

causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome; the second primary endpoint was the number of nights spent in the hospital per year. The primary safety outcome was a composite of death, stroke, or serious adverse events related to rhythm-control therapy. Secondary outcomes, including symptoms and left ventricular function, were also evaluated. The trial was stopped for efficacy after a median of 5.1 years of follow-up per patient. The patients in the early rhythm control were at a lower risk of primary-outcome event (hazard ratio, 0.79; 96% confidence interval, 0.66 to 0.94; P=0.005) and certain events such as death from cardiovascular causes (HR 0.72; 95% CI 0.52–0.98) and stroke (HR 0.65; 95% CI 0.44–0.97). Length of hospital stay did not differ significantly between the groups. Adverse events related to rhythm-control therapy occurred in 4.9% of the patients assigned to early rhythm control, the majority of adverse events included pharmacologically induced bradycardia.

Of note, patients with persistent AF made up only 26.0 and 27.3% of participants in the early rhythm group and usual care group respectively. Median days since AF diagnosis to the study inclusion was 36 days. Therefore, the results of this study can't be used in patients with long-standing AF. Information about AF relapses was not collected in both groups. The analysis of AAD used showed that the majority of patients didn't have structural heart disease in the rhythm control group. EAST-AFNET 4 differed from earlier studies, e.g. AFFIRM, as the patients showed significantly higher treatment adherence — 91.2% and 89.7% in the early rhythm control and usual care groups respectively. Also, important factors included rhythm control together with structured patients follow-up, optimal rate control, thorough risk factor modification and treatment of concomitant diseases. As such, both EAST-AFNET 4 and 2020 ESC guidelines describe that integrated approach towards AF management is highly effective.

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