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EURASIAN CLINICAL RECOMMENDATIONS ON DIAGNOSIS AND TREATMENT OF ATRIAL FIBRILLATION

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LIST OF ABBREVIATIONS

CAFÉ – complex atrial fractionated electrograms
EHRA – European Heart Rhythm Association
ESC – European Society of Cardiology
AAD – anti-arrhythmic drug
AV – atrioventricular
VKA – vitamin K antagonists
ACT – activated coagulation time
BP – blood pressure
ACG – anticoagulant
ACTh – anticoagulant therapy
ACE – angiotensin converting enzyme
ASS – acetylsalicylic acid
APTT – activated partial thromboplastin time
ARB – angiotensin receptor blocker
SCD – sudden cardiac death
ACP – accessory conduction path
GIB – gastrointestinal bleeding
GIT – gastrointestinal tract
IS – ischemic stroke
ICD – implantable cardioverter-defibrillator
CAG – coronary angiography
CV – cardioversion
PCC – prothrombin complex concentrate
PV – pulmonary veins
LV – left ventricle
LA – left atrium
INR – international normalized ratio
MRI – magnet resonance imaging
MSCT – multi-slice spiral computed tomography
LMWH – low molecular weight heparin
NOAC – new oral anticoagulants
NFH – non-fractionated heparin
ACS – acute coronary syndrome
DPACG – direct peroral anticoagulants
RCT – randomized controlled trials
RFA – radio frequency ablation
WPW syndrome – Wolff-Parkinson-White syndrome
GFR – glomerular filtration rate
STE – systemic thromboembolism
TIA – transient ischemic attack
AFL – atrial flutter
TEC – thromboembolic complications
ALA – auricle of left atrium
EF – ejection fraction
AF – atrial fibrillation
PCI – percutaneous coronary intervention
TE-ECHO-CG – transesophageal echocardiography
HR – heart rate
EST – external shock therapy
PM – pacemaker
EPI – electrophysiologic investigation
EchoCG – echocardiography

1. PREFACE

The present document provides the current recommendations on diagnosis and treatment of atrial fibrillation (AF). The recommendations were developed to help a physician select the optimum treatment strategy taking into account its possible influence on outcomes and also considering the benefit/risk ratio when using the methods for diagnosis and treatment of AF.

When developing the present recommendations, all participants of the task force following the principles of evidence-based medicine. The following classes of recommendations and levels of evidence were used to assess the practical significance and validity of suggested approaches (Tables 1 and 2).

To obtain the more detailed information, the participants of the task force recommend the readers to familiarize themselves with the current clinical recommendations on diagnosis and treatment of AF of the All-Russian Scientific Society of Arrhythmologists [1], European Society of Cardiology (ESC) [2], American Heart Association /American College of Cardiology [3].

The differences in the healthcare systems and provision of medical aid in different regions and also population and demographic peculiarities make it difficult to develop recommendations which could be fully fulfilled in all countries. These differences include among others the availability of drugs and means for non-drug treatment what is especially urgent for

Table 1. Classes of recommendations

Class	Definition
Class I	This method of treatment/diagnostic approach should be used, its benefit exceeds considerably concomitant risks
Class IIa	The use of this method of treatment/diagnostic approach is advisable, its benefit exceeds concomitant risks
Class IIa	This method of treatment/diagnostic approach may be used in certain situations, its benefit exceeds concomitant risks or is comparable with them
Class III	This method of treatment/diagnostic approach should not be used because it is not beneficial or can do harm

Table 2. Levels of evidence

Level	Evidence base
Level A	The evidences are obtained in several randomized controlled trials or meta-analyses of these trials
Level B	The evidences are obtained in one randomized controlled clinical trial or large-scale non- randomized trials
Level C	The clinical recommendation is based on the opinion (agreement) of experts/or results of small trials, register data

the Russian Federation and CIS countries. In particular, several original home anti-arrhythmic drugs: lappaconitin hydrobromede (trade name: Allapinin), diethylamino-propionyl-ethoxycarbonyl-aminophenothiazine (trade name: Ethacizine), 4-Nitro-N-[(IRS)-l-(4-fluorophenyl)-2-(l- ethylpiperidin-4-yl)ethyl] benzamide hydrochloride (trade name: Refralon), which are not used in other countries, are at our disposal.

2. ETIOLOGY AND EPIDEMIOLOGY OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common tachyarrhythmia form found in the general population in 2% of cases. The probability of AF increases considerably with age. AF is revealed in 3.8% of subjects aged above 60 years and in 9% of subjects older than 80 years [4].

Different AF types are distinguished: AF associated with cardiac valve affection (more often rheumatic mitral stenosis or mitral valve replacement, rarer tricuspid valve affection) and AF not associated with valve pathology.

When the valves are not involved, the main causes for development of AF include: essential hypertension, CHD, primary myocardial diseases, hyperthyroidism, pheochromocytoma, diabetes mellitus, alcohol abuse, body overweight, sleep apnea, hypokalemia, Wolff-Parkinson-White syndrome (WPW) and also other supraventricular reciprocal tachyarrhythmias [5-6]. There is data on genetic predisposition to AF [7-10]. More frequent development of AF in patients with broncho-pulmonary diseases is reported [11]. The atrial structural remodeling process develops in most cases in patients with AF; it is manifested by atrial enlargement revealed by echocardiographic investigation and magnet resonance imaging (MRI) of the heart and is represented morphologically by fibrosis, inflammatory infiltration, cardiomyocyte hypertrophy and their necrosis [12-13]. The thorough clinical and instrumental investigation cannot reveal any cardiac or non-cardiac factors of AF development in 30% of cases [14-15].

3. DEFINITION AND CLASSIFICATION OF ATRIAL FIBRILLATION

Atrial fibrillation is supraventricular tachyarrhythmia characterized by chaotic electric atrial activity with high rate (from 300 to 700 per minute – ff waves in Fig. 1) and irregular ventricular rhythm (provided there is no total atrioventricular [AV] block).

Depending on ventricular rate when keeping wake, the following variants are distinguished:

- normosystolic AF variant (the rate in the range from 60 to 100 per minute);
- tachysystolic AF variant (the rate of more than 100 per minute, see Fig. 1-A);
- bradysystolic AF version (the rate of less than 60 per minute, see Fig. 1-B).

The reversible transitions from one AF variant to another are observed usually depending on the physical activity level, emotional tension degree and also under the action of drugs and some other factors influencing the functional characteristics of the AV node.

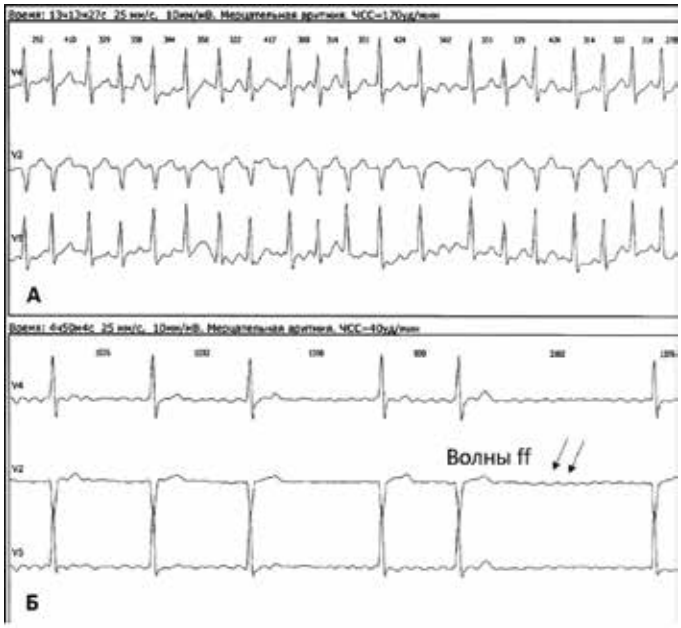

Figure 1. Atrial fibrillation. A. – tachysystolic variant, B. – bradysystolic variant. ff waves are designated by arrows.

The modem classification distinguishes five AF types out of which the latter four types are designated also as forms of the clinical course: (1) newly diagnosed (revealed) AF, (2) paroxysmal AF, (3) persistent AF, (4) long-standing persistent AF and (5) permanent or chronic AF.

1) **Newly diagnosed (revealed) AF**: any AF recorded for the first time irrespective of arrhythmia duration.
2) **Paroxysmal AF**: repeatedly occurring (2 and more episodes) AF which stops spontaneously within 7 days after the attack onset. AF stopped by medicinal or electric cardioversion within 48 hours after arrhythmia onset is also referred to paroxysmal form.
3) **Persistent AF**: newly revealed or repeatedly occurring AF lasting for more than 7 days, which cannot stop spontaneously and requires electric or medicinal cardioversion for its removal.
4) **Long-standing persistent AF**: AF lasting for more than a year if a decision is mode to recover the sinus rhythm with the help of cardioversion or radical intervention (catheter ablation) and/or surgical treatment.
5) **Permanent AF**: arrhythmia with duration of more than 7 days if attempts to stop it are ineffective or a decision is made that it is not necessary to recover and preserve the sinus rhythm

because of some or other causes. The latter means the refusal from cardioversion or other methods for intervention or surgical treatment aimed at normalization of the cardiac rhythm.

A paroxysm recurrence period precedes usually the establishment of the permanent form. Not infrequently different arrhythmia forms can be combined in one patient at different diseases stages. The prevalent AF form is indicated in diagnosis in such cases.

The cases are not infrequent when it is not possible to reveal an underlying cardiac disease or other factors predisposing to arrhythmia in subjects with AF. Such patients traditionally received a diagnosis of idiopathic AF (or "lone atrial fibrillation" in English literature) [15]. At present it is not recommended to use such wording but the above classification of AF shall be applied.

4. PATHOGENETIC MECHANISMS OF ATRIAL FIBRILLATION

The availability of three components is necessary for stable AF to occur: 1) starting (trigger) factors of arrhythmia, 2) arrhythmogenic substrate of arrhythmia providing for spontaneous maintenance of AF and also 3) individual modulating effects increasing the susceptibility of the arrhythmogenic substrate to trigger factors of AF [16-17].

In overwhelming majority of cases (95%) the pathologic electric activity in the ostia of the pulmonary veins is the starting factor (trigger) for AF. The trigger activity or excitation re-entry in muscle fibers lining the ostia of the pulmonary veins in the points of their flowing in the atria are the electrophysiologic mechanisms of such focal activity [18-20]. This activity is manifested in ECG in the form of frequent early atrial extrasystoles of "P-on-T" type and/or runs of atrial tachycardia (Fig. 2).

Extrasystoles from the venae cavae and also atrial extrasystoles from different regions of both atria are rarer trigger factors of AF. AF can be induced by electric stimulation of the atria when performing the intracardiac electrophysiologic investigation (EPI).

The arrhythmogenic substrate of AF represents the structurally and functionally changed (remodeled) atrial myocardium providing for stable spontaneous maintenance of AF. Remodeling is understood as the totality of pathologic processes occurring in the atria in response to onset of AF and/or as a result of other acting etiologic factors. Remodeling starts from disturbed ion cellular mechanisms of pulse formation and ends with the structural and functional degradation of the atrial myocardium and atriomegaly. The basic structural changes in the atrial myocardium predisposing to formation of AF substrate are fibrosis, inflammation, cardiomyocyte apoptosis and hypertrophy. Functional disturbances in the atrial myocardium include occurrence of heterogeneity of pulse conduction velocities in different directions and also dispersion of repolarization processes in the atrial myocardium. AF progression and arrhythmia resistance to medicinal and intervention treatment are determined as a rule by the degree of atrial remodeling processes [21-22].

5. CLINICAL SYMPTOMS IN PATIENTS WITH ATRIAL FIBRILLATION

Typical symptoms of AF are: intensified and, as a rule, arrhythmic heartbeats, palpitations, dyspnea, undue fatiguability, low exercise tolerance and hyperhidrosis. It is recommended to use the EHRA symptom score (European Heart Rhythm Association; Tables 3 and 4) in order to assess the significance of clinical signs of AF [23]

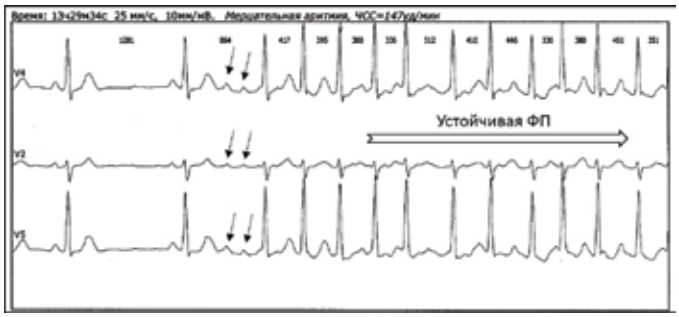

Figure 2. Occurrence of atrial fibrillation due to frequent ectopic activity from the ostium of the pulmonary vein. Key: frequent ectopic activity from the ostium of the pulmonary vein is designated with arrows.

[23]. In accordance with it, 25-40% of patients have asymptomatic or low-symptomatic course of AF while 15-30% of patients report greatly pronounced or disabling symptoms [24-25].

AF is the cause for one third of all hospitalizations because of cardiac rhythm disorders. The main causes for hospitalization in AF include the necessity of emergency stopping of AF because of distressing symptoms, rarer because of acute hemodynamic instability, acute coronary syndrome, onset and progression of heart failure, thromboembolic complications. AF is associated with double increase of the risk of death, first of all, cardiac death irrespective of availability of other risk factors [28].

The most dangerous complications of AF are thromboembolic complications including transient ischemic attack (TIA) of the brain, ischemic cardioembolic stroke (onset of AF in patients without cardiac valve involvement increases the risk of stroke 5 times and such risk is increased 17 times in case of valvular disease), thromboembolism of the extremities vessels and infarctions of the internal organs. Besides that, AF can be a cause for cognitive dysfunctions including vascular dementia. The patients with AF have worsened life quality, lowered exercise tolerance; left ventricular dysfunction occurs and/or progresses not infrequently with development of heart failure [29-31].

6. DIAGNOSIS AND SCREENING OF ATRIAL FIBRILLATION

AF is diagnosed basing on recording arrhythmia in ECG. Long-term ECG monitoring (from 24 hours to 7 days), the use of portable ECG-recorders with the possibility to transfer ECG by phone and also implantable ECG-recorders with "loop memory" are required not infrequently in order to confirm the diagnosis of paroxysmal AF. To make a diagnosis it is necessary to record an arrhythmia episode lasting for more than 30 seconds. The atrium programmed stimulation during EPI for confirming the diagnosis of AF is not performed because of low sensitivity and specificity of the method regarding reproducibility of clinically significant AF [32-33].

The typical ECG-signs of AF are the following: absence of P-wave, presence of polymorphous ff-waves with different amplitude changing from one into another without clear isoline between them and also absolute chaotic state and irregularity of the ventricular rhythm (see Fig. 1). The latter sign is not recorded in AF with simultaneous AV-block of degree III (in case of the so-called Frederick phenomenon).

Arrhythmia may be asymptomatic and is revealed accidentally at a medical examination approximately in one fourth of cases what indicates advisability of AF screening in patients with high risk. Clinical recommendations for diagnosis and screening of AF are presented in Table 5.

Table 3. EHRA symptom score

EHRA class	Description
I	AF does not cause symptoms
IIa	The normal daily activity is not disturbed by symptoms associated with AF
IIb	Moderately pronounced symptoms: sensations associated with AF trouble a patient but the normal daily activity is not disturbed
III	Pronounced clinical symptoms: the normal daily activity is disturbed by the symptoms caused by AF
IV	Invalidizing clinical symptoms. The normal daily activity is impossible.

Table 4. Recommendations for the use of the modified EHRA symptom score

Recommendations	Class	Level	Reference
It is recommended to use the modified EHRA scale in the clinical practice and research work in order to assess the symptoms caused by AF	I	C	26, 27

Table 5. Recommendations for diagnosis and screening of AF

Recommendations	Class	Level	Reference
Arrhythmia should be documented by ECG in order to verify diagnosis of AF	I	B	34
Purposeful screening for revealing AF by palpatory pulse assessment or ECG recording is recommended in subjects aged above 65 years	I	B	35-37
For patients with history of TIA or ischemic stroke, it is recommended to perform screening using short-term ECG recording with subsequent ECG monitoring for at least 72 hours in order to reveal AF	I	B	38-39
It is recommended to investigate diagnostic data of pacemakers (PM) and implantable cardioverters-defibrillators (ICD) on regular base in order to reveal episodes of rapid atrial rhythm. For patients with episodes of rapid atrial rhythm, the diagnosis of AF should be confirmed by ECG recording/ ECG monitoring before prescription of the treatment for AF	I	B	40-41
For patients with history of ischemic stroke, it is advisable to perform ECG monitoring using noninvasive monitors or implantable loop recorders in order to reveal asymptomatic AF	IIa	B	42-43
Systematic ECG screening for revealing AF may be used in patients with high risk of stroke or those aged above 75 years	IIb	B	44-46

7. INVESTIGATION OF PATIENTS WITH ATRIAL FIBRILLATION

AF develops often in patients with cardiovascular diseases which were not diagnosed earlier, therefore, all patients with newly revealed AF (possibly, except for situations when development of AF is associated with a clearly established causative factor, e.g., alcohol abuse, thyrotoxicosis) need the extended cardiologic investigation.

In all patients with AF it is necessary to obtain the detailed history, elucidate concomitant diseases, determine AF form and assess the risk of stroke (see below), estimate the degree of clinical symptoms of AF and its complications such as thromboembolism and left ventricular dysfunction.

ECG recording at the time of patient's complaints of arrhythmic heartbeats is recommended to verify the supposed but not established diagnosis of AF. Changes in ECG intervals and their dynamics are of great importance for assessing safety of anti-arrhythmic pharmacotherapy.

The complete blood count (ruling out an acute inflammatory process), biochemical blood analysis (assessment of renal function and electrolyte disturbances), measurement of serum thyroid-stimulating hormone (exclusion of thyrotoxicosis) are advisable in order to reveal more precisely a possible cause of AF.

Transthoracic echocardiography is recommended in all patients for revealing the structural cardiac pathology (valvular defects) and assessing myocardium thickness, cavity size and systolic function of the left ventricle (LV), atrium size, function of the right cardiac chambers. Transesophageal echocardiography is used for more detailed assessment of the valvular heart apparatus in order to rule out intracardial thrombosis (especially, in the auricle of the left atrium) before cardioversion [47].

ECG monitoring in outpatient settings is performed for revealing supposed AF, assessing the efficiency and safety of anti-arrhythmical pharmacotherapy and pharmacotherapy slowing the cardiac rhythm.

For patients with clinical symptoms of angina pectoris it is advisable to perform the investigation to confirm or rule out the diagnosis of coronary heart disease; such investigation is to be performed in accordance with clinical recommendations.

Multi-slice spiral computed tomography (MSCT) of the heart with contrast enhancement is advisable for assessing anatomy of the pulmonary veins before a planned invasive intervention (catheter ablation – see below). This method allows also to assess anatomy and atherosclerotic lesions of the coronary arteries, reveal thrombi in the cavities or auricles of the atria.

Cerebral MRI may be helpful in order to rule out the past ischemic stroke taking into account clinical symptoms, changes in the neurologic status.

The recommendations on primary investigation of patients with AF are presented in Table 6.

8. TREATMENT

8.1. General principles

The treatment of AF includes both the measures aimed at improvement of the patient's prognosis (anticoagulant therapy, correction of the cardiovascular pathology) and the measures for relief of symptoms (control of the heart rate and rhythm). It is important to emphasize that a complex of general recommendations and anticoagulant therapy have the maximum effect of the disease prognosis what should be obligatorily explained to a patient because the benefic of these measures may be not evident for a patient. It should be mentioned that efficiency of anti-arrhythmical pharmacotherapy and intervention methods for treatment of AF is moderate and it is considerably inferior to the efficiency of catheter ablation in paroxysmal supraventricular tachycardias. The explanation of the expected efficiency of the treatment to patients allows to prevent unjustified expectations and can enhance compliance for the treatment.

If a potentially reversible cause for AF (e.g., revealing electrolyte disorders, detection of valvular heart disease etc.) is found, removal of this cause can promote the recovery of the sinus rhythm and prevention of AF recurrences in future (Table 7).

In principle, there exist two strategies for the treatment of patients with AF:

1) "control of heart rate": decrease of ventricular contraction rate in settings of preserved AF meaning withholding from anti-arrhythmic treatment as such; in this situation AF itself may have paroxysmal, persistent or permanent course;
2) "control of rhythm": recovery (if necessary) and maximum possible long-term preservation of the sinus rhythm by means of the drug and/or non-drug anti-arrhythmic treatment. Administration of the anti-arrhythmic treatment does not free from the need to "control heart rate" because there always exists probability of AF recurrence which should not develop with excessively high ventricular rhythm.

It should be mentioned that large clinical trials did not show advantages of any of these strategies regarding the lifespan and cardiovascular complications. The strategy for treatment of AF is selected individually depending on the nature of arrhythmia course, degree of clinical symptoms, presence of concomitant diseases, tolerance of different drug groups and with obligatory consideration of the attending physician's opinion and patient's preference.

8.2. The control of heart rate using drugs

Such tactics is more preferable in patients with asymptomatic or low-symptomatic AF, with inefficient preceding attempts of preventive anti-arrhythmic treatment and long course of arrhythmia (persistent and permanent forms). These tactics used in patients with AF paroxysms, which developed recently and have an established cause, may favor time gain and improve the patient's wellbeing while the removal of the causative factor (e.g., correction of electrolyte disorders, compensation of respiratory failure, treatment of thyrotoxicosis) may result in delayed recovery of the sinus rhythm.

Beta-adrenergic blockers and calcium channel blocking agents – Verapamil and Diltiazem (they are contraindicated in case of lowered left ventricular ejection fraction) are usually the drugs of the first line. If they are not effective, it is possible to add Digoxin (it should be taken into account that administration in combination with Verapamil increases toxicity). Monotherapy with Digoxin is used rarely because of long period for development of the therapeutic effect and less pronounced decrease of the heart rate (HR) during physical activities as compared to beta-adrenergic blockers.

Table 6. Recommendations on primary investigation of patients with AF

Recommendations	Class	Level	Reference
Full investigation including thorough obtaining of the history, clinical investigation and diagnosis of concomitant diseases is recommended in all patients with AF, especially in patients with newly revealed arrhythmia and in patients having dramatic negative changes in the form of increased frequency of attack recurrence and their duration.	I	C	48
Transthoracic echocardiography is recommended in all patients with AF to rule out/confirm structural cardiac disease, reveal left ventricular systolic dysfunction associated wit AF and also assess the size of cardiac chambers.	I	C	49
The complete blood count (ruling out an acute inflammatory process), biochemical blood analysis (assessment of renal function and electrolyte disturbances), measurement of serum thyroid-stimulating hormone (exclusion of thyrotoxicosis) are advisable in order to reveal more precisely a possible cause of AF.	I	C	50
It is recommended to assess the renal function basing on the serum creatinine level and creatinine clearance in all patients with AF in order to reveal renal diseases and correct drug doses.	I	A	51-52
The annual assessment of the renal function is advisable for revealing chronic kidney disease or assessing its progression in all patients with AF receiving new oral anticoagulants.	IIa	B	53
ECG monitoring in outpatient settings is helpful for elucidation of the association of clinical symptoms with AF paroxysms. It is also recommended to assess the efficiency and safety of anti-arrhythmical pharmacotherapy and pharmacotherapy slowing the cardiac rhythm.	IIa	C	54
The detailed interview for revealing clinical symptoms and, if necessary, the investigation in order to confirm/rule out obstructive sleep apnea/ hypapnea syndrome should be performed in all patients with AF	IIa	B	55-56

If other drugs are ineffective and also in case of AF in patients with heart failure and lowered left ventricular ejection fraction, it is possible to use Amiodarone (it is necessary to take into account the possibility of sinus rhythm recovery and also probability of side effects caused by the drug in case of long-term intake).

Recommendations on the tactics foe drug control of HR are presented in Table 8.

8.3. The recovery of the sinus rhythm

The recovery of the sinus rhythm is advisable in patients with pronounced clinical symptoms and poor arrhythmia tolerance, if it is impossible to control adequately the ventricular contraction rate and in situations when adequate control of the ventricular contraction rate is not accompanied with condition improvement (e.g., pronounced symptoms of AF are preserved or signs of heart failure develop).

In relatively rare cases of uncontrolled tachycardia accompanied with progressing heart failure and/or coronary insufficiency or if these signs are preserved in spite of adequate slowing of ventricular contraction rate, it may become necessary to recover the sinus rhythm in critical situations notwithstanding the persistency of arrhythmia for more than 48 hours and absence of adequate anticoagulant therapy.

AF is associated with risk of thrombus formation in the atrial auricles and cavities and development of cardioembolic complications. Therefore, the tactics for providing aid is determined not only by clinical symptoms but also by the length of the current paroxysm. The sinus rhythm may be recovered by any way without preceding anticoagulant preparation only if the duration of the current paroxysm does not exceed 48 hours. It is recommended to abstain from undelayed recovery of the sinus rhythm in patients with asymptomatic AF paroxysms and in situations when it is difficult for a patient to report the duration of the current paroxysm.

Many AF paroxysms may be stopped spontaneously within several hours, therefore, when a patient with recent-onset paroxysm without hemodynamic instability seeks medical attention, initial use of the drugs slowing the ventricular contraction rate will favor improvement of the patient's condition and can allow to escape the necessity to administer drug or electric cardioversion. As electrolyte balance disturbance (e.g., because of intestinal infection, alcohol intoxication or use of diuretics) is one of the factors provoking AF intravenous administration of potassium preparations (if there no contraindications, i.e. severe renal failure, hyperkalemia etc.) may be helpful at this stage.

In situations when AF is caused by any transient and potentially reversible factor (high fever, thyrotoxicosis, alcohol intoxication etc.), the treatment of the underlying disease also may favor spontaneous sinus rhythm recovery. In this situation the sinus rhythm recovery by drug or electric cardioversion is not advisable because of high risk of early AF recurrence before removal of its cause (normalization of the thyroid status, decrease of the body temperature etc.).

Stopping of long AF paroxysms (lasting for more than 48 hours) and sinus rhythm recovery in persistent form of the disease should be performed with simultaneous administration of adequate anticoagulant therapy (preceding intake for not less than 3 weeks or the need to rule out presence of thrombi in the cavities and auricles according to findings of transesophageal echocardiographic investigation). After sinus rhythm recovery there exists the risk of de novo thrombus formation associated with transient disturbance of atrial function ("atrial stunning" phenomenon), therefore, all patients should receive anticoagulant therapy for not less than 4 weeks irrespective of the risk of cardioembolic complications as per CHA_2DS_2-Vasc score (see below).

There exist two methods for recovery of the sinus rhythm: external shock therapy (EST) and pharmacologic cardioversion. The efficiency of EST is 70-90%. The procedure is performed under short-term general anesthesia, therefore, it is conducted after fasting. Biphasic synchronized shocks with power of 150 J are used the most often. In case of inefficiency, it is possible to apply another shock of 170 J. Shock with lower power (from 50 J) are used usually to stop atrial flutter (ATF). EST is a method of choice in situations when arrhythmia is associated with hemodynamic instability because of rapid rhythm recovery. The use of EST with simultaneous maintenance anti-arrhythmic therapy (most often, with anti-arrhythmic drugs of Class III) enhances the procedure efficiency and lowers the risk of AF recurrences after sinus rhythm recovery.

Except for Refralon (see below), the efficiency of most anti-arrhythmic drugs used for pharmacologic cardioversion is inferior to efficiency of EST but this method does not require general anestesia/sedation. The drug should be selected taking into account possible contraindications and side effects of the drug, information about efficiency of drugs in stopping of previous paroxysms, data on drug taken by a patient. The drug used for stopping also has a preventing effect regarding possible early arrhythmia recurrences. The anti-

Table 7. Recommendations on etiotropic treatment of atrial fibrillation

Recommendations	Class	Level	Reference
The correction of the thyroid status in patients with AF developed in association with thyrotoxicosis favors decrease of the heart rate in the setting of arrhythmia and recovery of the sinus rhythm	I	B	60
The correction of hypoxemia and acidosis should be considered as the initial treatment in patients with AF which developed during the acute or exacerbation of chronic pulmonary disease.	IIa	C	57
The measures for reduction of the body weight in patients with obesity are helpful for relief of symptoms and decrease of AF recurrence frequency.	IIa	B	58-59
The treatment of obstructive sleep apnea is helpful in order to prevent AF recurrences	IIa	B	61-62
Early surgical correction of mitral valve disease is advisable in patients with severe mitral regurgitation, preserved LV function and newly revealed AF, even when there are not symptoms, especially, if valve plasty is possible	IIa	C	63
Mitral valvulotomy is helpful is patients with severe mitral stenosis, suitable anatomy and newly revealed AF	IIa	C	63

Table 8. Recommendations on the tactics for control of heart rate using drugs

Recommendations	Class	Level	Reference
Beta-adrenergic blockers, Digoxin, Diltiazem or Verapamil are recommended for control of HR in case of AF in patients with LV ejection fraction (EF) ≥ 40%.	I	B	64-66
Beta-adrenergic blockers and/or Digoxin are recommended for control of R in case of AF in patients wit LV EF < 40%.	I	B	64-66
The decrease of the pulse rate at rest to < 110 beats/min is recommended as the initial target; further decrease of HR is advisable in case of poor arrhythmia tolerance and/ or LV EF lowering, development of clinical signs of congestive heart failure	IIa	B	67
The combined therapy (including different drugs influencing HR) is helpful if the use of one drug does not allow to achieve the target HR values	IIa	C	64-66
Amiodarone may be used for control of HR when providing the acute care in patients with instable hemodynamics or significantly lowered LV EF	IIb	B	3
Anti-arrhythmic drugs of classes I and III should not be used permanently to control HR in patients with permanent AF form (in such cases when it is not planned ti recover the sinus rhythm)	III	A	2
Intravenous administration of Verapamil, Diltiazem and Digoxin is contraindicated in case of AF paroxysms in patients with WPW syndrome, because they can improve conduction via Kent bundle	III	A	68-70

arrhythmic drugs used for stopping can promote transformation of AF to AFL what can be associated with increase of the ventricular contraction rate and worsening of the patient's condition (up to development of hemodynamic instability), therefore it is preferable to perform a procedure of pharmacologic cardioversion at the intensive care unit.

Procainamide (Novocainamide), the drug of class IA, is used the most often as a drug for stopping AF paroxysms. In spite of its use for a long period, there were no large-scale clinical trials of its efficiency and safety. The drug is contraindicated for patients with structural heart disease, severe conduction disturbances. Decrease of BP, risk of ventricular arrhythmogenic action should be mentioned among its side effects. The data is available on lowered efficiency when the duration of the paroxysm being stopped increases.

When administered intravenously, Propafenone, the drug of class IC, has high efficiency in stopping AF paroxysms and quite rapid action (as a rule, paroxysms are stopped within 30 minutes – 2 hours after administration of the drug). Peroral intake of Propafenone in the dose of 450–600 mg also stops AF paroxysms efficiently but within a longer period (usually within 2–6 hours). Such method for use of Propafenone is called "tablet in the pocket". Taking into account the higher risk of side effects caused by the drug when it is taken in a higher dose, the use of the strategy "tablet in the pocket" is recommended only if safety of administration of the higher drug dose was assessed earlier at the hospital. Propafenone is contraindicated to patients with CHD and patients with structural heart disease. It can provoke bronchospasm in rare cases in patients with severe asthma because of beta-blocking action. It can cause transformation of AF to AFL what may be associated wit R increase and worsening of the patient's condition.

Intravenous infusion of Amiodarone, the drug of class III, is also highly effective (up to 90% in paroxysms lasting for not more than 48 hours) regarding the sinus rhythm recovery but a paroxysm is stopped several hours later than in case of administration of Procainamide or Propafenone. The drug lowers the ventricular contraction rate during an AF paroxysm; this effect develops more rapidly.

Refralon is a newly developed Russian anti-arrhythmic drug of Class III, which is administered intravenously. The drug is used in the starting dose of 10 μg/kg (slow injection during 3-5 minutes). If arrhythmia is preserved for 15 minutes repeated injections of the drug are possible as per the regimen: 10 μg/kg – 10 μg/kg – 10 μg/kg with 15 min-intervals. The maximum total dose is 30 μg/kg. It is possible to divide the first administered dose in 2 injections (regimen: 5 μg/kg – 5 μg/kg – 10 μg/kg – 10 μg/kg) in order to enhance safety. The administration of the drug is stopped at any stage in the following cases: sinus rhythm recovery; decrease of HR to < 50 beats/min; increased duration of QT interval (≥ 500 ms); occurrence of proarrhythmic effects.

In contrast to other anti-arrhythmic drugs, Refralon allows to recover the sinus rhythm in patients with not only paroxysmal but also with persistent AF forms and in this case the drug efficiency is comparable with EST (about 90%). The effect lasts for about 24 hours (arrhythmia is stopped within 3 hours in most cases). Similar to other drugs of Class III, the main adverse effect consists in increased duration of QT interval and risk of arrhythmogenic action (torsade depointes; risk is about 1%), therefore, Refralon may be used only at intensive care units with telemetric ECG control for up to 24 hours.

AF and AFL paroxysms in patients with WPW syndrome deserve special consideration because in case of low refractivity of accessory conduction paths paroxysms develop with very high HR, are associated with hemodynamic instability and can be transformed to life-threatening ventricular arrhythmias, therefore, they may require immediate EST.

Intravenous administration of Procainamide or Amiodarone may be used to stop arrhythmia in patients with AF or AFL paroxysms with conduction via Kent bundle not associated with hemodynamic instability. Besides that, these drugs decrease HR during a paroxysm by inhibiting conduction via the accessory conduction path what also favors the patient's condition improvement.

As Verapamil, Diltiazem and Digoxin, when administered intravenously, can improve conduction via Kent bundle, these drugs are contraindicated in case of AF paroxysms in patients with WPW syndrome [68-70].

8.4. Prevention of atrial fibrillation recurrences using anti-arrhythmic drugs (maintenance anti-arrhythmic therapy)

Administration of anti-arrhythmic drugs (AAD) for prevention of AF recurrences (paroxysmal and persistent AF, after cardioversion) is used when a patient has strongly pronounced arrhythmia symptoms which are poorly removed by agents for heart rate control. Such prophylaxis is performed by regular long-term administration of anti-arrhythmic drugs of class I (Allapinin in the dose of 75–150 mg/day, Propafenone in the dose of 450–1200 mg/day, Ethacyzin in the dose of 150 mg/day etc.) and Class III (Sotalol in the dose of 160–320 mg/day, Amiodarone in the dose of 200 mg/day).

AAD of Class I are contraindicated for patients with structural heart diseases, disturbed left ventricular systolic function (left ventricular ejection fraction of 40% and less), with any signs of heart failure, any forms of coronary heart disease (irrespective of clinical symptoms of the disease and performing revascularization) and also in case of left ventricular myocardium hypertrophy equal or exceeding 15 mm according to findings of echocardiography.

Sotalol may be used for prevention of AF recurrences in patients with structural heart disease, CHD. It is not recommended to use the drug if pronounced myocardium hypertrophy (these patients often have increased duration of QT interval, therefore, there exists higher risk of ventricular arrhythmogenic action of the drug), chronic heart failure and renal failure are present.

Amiodarone is the only drug allowed for use with the purpose of prevention of AF recurrences in patients with heart failure. In other cases Amiodarone should not be used as a drug of the first choice because of the significant number of no-cardiac side effects.

AAD can promote aggravation of cardiac conduction disorders and have an proarrhythmic action even in patients having no contraindications for their use. Just therefore, when administering the drug anti-arrhythmic therapy, it is obligatorily to control the efficiency and safety of the treatment including sequential ECG control during the first 24 hours of the treatment and, preferably, Holter ECG monitoring.

Recommendations on administering the maintenance anti-arrhythmic therapy are presented in Table 10.

8.5. The role of non-anti-arrhythmic drugs in prevention of atrial fibrillation recurrences

Renin – angiotensin – aldosterone system blockers (angiotensin converting enzyme [ACE] inhibitors and angiotensin receptor blockers [ARB]) prevent AF in patients with heart failure and essential hypertension (especially if left ventricular hypertrophy is present). Limited data is available that the use of these drugs can favor enhancement of the efficiency of cardioversion and maintenance anti-arrhythmic therapy. It is not recommended to administer these drugs to patients with AF without concomitant cardiovascular diseases (essential hypertension, post-infarction cardiosclerosis, heart failure) (Table 11).

8.6. No-drug treatment of AF

Since the time of the first description of triggers in the pulmonary veins initiating paroxysmal AF [85], catheter ablation of AF has turned from a specialized experimental procedure into a common method for treatment and prevention of AF recurrences [86-87].

8.6.1 Indications for catheter ablation

Catheter ablation is recommended for patients with symptomatic paroxysmal AF [indication class I, A] or symptomatic persistent AF [indication class IIa, B], which is resistant to at least one anti-arrhythmic drug of class I or III [88]. Such practice is justified by the results of randomized trials in which ablation led to improved control of the cardiac rhythm as compared to anti-arrhythmic drugs. Meta-analysis of the studies involving mainly patients with paroxysmal AF demonstrated also evident advantage of catheter ablation as compared to the anti-arrhythmic therapy [89-90].

The results of the studies which compared directly anti-arrhythmic drugs or catheter radio frequency ablation (RFA) as therapeutic

Table 9. Recommendations on sinus rhythm recovery

Recommendations	Class	Level	Reference
Electric cardioversion is recommended for sinus rhythm recovery in patients with acute hemodynamic instability	I	B	1-3
Sinus rhythm recovery (by means of EST or pharmacologic cardioversion) is recommended in patients with paroxysmal, persistent or long-standing persistent AF forms with clinical symptoms as part of the rhythm control strategy.	I	B	1-3
Administration of Refralon may be used as an alternative to scheduled EST in order to recover sinus rhythm including cases with persistent and long-standing persistent course of AF and AFL.	I	B	71-75
Propafenone is recommended for pharmacologic cardioversion of short-term AF paroxysms in patients without CHD or structural cardiac pathology.	I	A	76-77
When making a choice between EST and pharmacologic cardioversion, one should be guided by patient's and physician's preferences except for AF associated with hemodynamic instability	IIa	C	1-3
Preliminary treatment with Amiodarone, Sotalol or Propafenone should be considered in order to enhance the efficiency of electric cardioversion and prevent AF recurrences	IIa	B	1-3
A single peroral administration of Propafenone in the dose of 450-600 mg ("tablet in the pocket" approach) is advisable in some patients with short-term (up to 48 hours) AF paroxysm and without any concomitant structural heart disease or CHD for sinus rhythm recovery provided that safety of such treatment is assessed preliminarily with ECG control in inpatient settings.	IIa	B	78-79
Amiodarone is recommended for cardioversion of AF in patients with CHD and/or structural heart disease.	I	A	80
Amiodarone is recommended for pharmacologic cardioversion of AF in patients with CHD and/or structural heart disease.			

Table 10. Recommendations on prevention of atrial fibrillation recurrences using anti-arrhythmic drugs

Recommendation	Class	Level	References
AAD should be selected thoroughly taking into account presence of concomitant diseases, risk of side effects of the drugs and patient's preference	I	A	1-3
Allapinin, Ethacyzin Propafenone or Sotalol are recommended for prevention of AF recurrences in patients without structural heart disease	I	A	1-3
Amiodarone is recommended for prevention of AF recurrences in patients with heart failure	I	B	1-3
Amiodarone is more effective in prevention of AF recurrences than other AAD but has non-cardiac side effects, risk of which becomes higher as the drug dose and duration of its use increase. Therefore, other AAD and intervention treatment of AF should be considered in the first place	IIa	C	1-3
The patients receiving the maintenance anti-arrhythmic therapy should undergo a periodic examination in order to assess safety of the administered treatment	IIa	C	1-3
Sequential ECG control with assessment of PQ, QRS and QT interval duration is recommended to estimate safety of the treatment during the first 24 hours of anti-arrhythmic therapy; it is preferable also to perform Holter ECG monitoring at day 2-3 of the treatment.	IIa	B	1-3
PM implantation and prescription of the maintenance anti-arrhythmic therapy are advisable in patients with recurring AF course associated with pronounced clinical symptoms, in case of sinus node dysfunction or atrioventricular conduction disorder, if there are contraindications for the intervention AF treatment or in case of refusal from it	IIa	B	1-3
The maintenance anti-arrhythmic therapy during the "blind period" (90 days) after the intervention treatment of AF is helpful to maintain the sinus rhythm because of high risk of early AF recurrences	IIa	B	1-3
The maintenance anti-arrhythmic therapy is contraindicated for patients with significant sinus or AV node dysfunction (without permanent PM), increased QT interval (> 480 ms for AAD of Class III)	III (harm)	C	1-3

methods of the first line in patients with paroxysmal AF are limited [91] but the available data show higher efficiency of ablation [92]. Ablation may be considered as a therapeutic method of the first line, i.e. without previous administration of AAD [recommendation class II, B/C] taking into account the high probability of cardiac rhythm control with the help of catheter ablation in patients with paroxysmal AF and minimum signs of heart affection and also relative safety of this method (if the procedure is performed at the center having the sufficient experience). The data on efficiency of catheter ablation for treatment of long-standing persistent (more than 1 year) AF is insufficient [recommendation class IIb, C] [88].

The studies CASTLE [93], AATAC [94], CAMERA-MRI [95] showed superiority of catheter ablation as compared to the drug treatment in patients with AF with lowered LV ejection fraction and heart failure. After catheter ablation patients have confidently increased EF, decreased number of hospitalizations and mortality. Catheter ablation in this patient category is indicated with recommendation class IIa (B) [96]. It should be mentioned that the latest large-scale randomized study CABANA, in which one third of patients with AF had heart failure of class II-III as per New-York classification, did not demonstrate superiority of catheter ablation regarding lowered risks of death, stroke and bleedings as compared to anti-arrhythmic therapy [97].

At present intracardiac catheter RFA and balloon cryoablation (cryoisolation) of pulmonary veins are the most common types of intervention treatment of AF.

8.6.2. Preparation of patients for catheter ablation

The preoperative preparation to isolation of the pulmonary veins is of great importance for safe performing of the procedure and should include:

1) Obligatory methods foe investigation of a patient (complaints, history, complete blood count and biochemical blood analysis, coagulogram, ECG, echocardiography (EchoCG), Holter ECG monitoring);
2) Additional investigation methods: blood test for thyroid hormones, computed tomography of the heart with contrast enhancement (if possible), ECG stress test or stress echocardiography and also coronary angiography if necessary;

Table 11. Recommendations on the use of non-anti-arrhythmic drugs for prevention of atrial fibrillation recurrences

Recommendation	Class	Level	References
ACE inhibitors, ARB and beta-blockers are advisable for prevention of AF in patients with heart failure and lowered left ventricular ejection fraction	IIa	A	81-82
ACE inhibitors or ARB are advisable to prevention of AF in patients with essential hypertension, especially if left ventricular hypertrophy is present.	IIa	B	83
The treatment with ACE inhibitors or ARB may be considered in patients with AF recurring after cardioversion or with simultaneous administration of AAD	IIb	B	84
It is not recommended to administer ACE inhibitors or ARB for prevention of AF recurrences in patients without concomitant cardiovascular diseases (essential hypertension, post-infarction cardiosclerosis, heart failure)	III (harm)	B	1-3

3) Obligatory anticoagulant therapy: vitamin K antagonists (target INR values 2-2.5) or new oral anticoagulants (NOAC) (Apixaban, Dabigatran, Rivaroxaban) shall be administered 3-4 weeks before the surgery. For young patients with ectopic (focal) AF form and low risk of thromboembolic complications (CHADS2VASC (see below)score 0-2), the duration of anticoagulant therapy may be reduced provided that left atrium thrombosis is ruled out by transesophageal or intracardiac echoCG or computed tomoangiography. In order to reduce the risk of bleedings it is possible to withdraw NOAC 24 hours (Rivaroxaban) or 12 hours (Apixaban, Dabigartan) before the procedure [98-100].
4) Catheter ablation may be performed with simultaneous administration of the drugs of NOAC group: Dabigatran [recommendation class I, A] and Rivaroxaban [recommendation class I, B]. Heparin is administered intravenously under control of ACT (blood clot formation time) (not less than 300-350 s) during catheter ablation.
5) It is recommended to resume the therapy with NOAC not later than 3-5 hours after completion of catheter ablation to exclude hemopericardium and risk of other potential bleedings [88].

8.6.3. Technique of catheter ablation

Full isolation of the ostia of the pulmonary veins (PV) [recommendation class I, A] as the main trigger factor for AF [88] is the most important and in a significant number of cases also a sufficient goal of catheter ablation in patients with both paroxysmal and persistent AF form. This goal can be achieved using catheter isolation of the ostia of the pulmonary veins with the help of radio frequency energy (RFA) or balloon cryoablation (Fig. 3). Isolation of the pulmonary veins can be achieved in case of extended (antral) circular isolation of the pulmonary veins using navigation non-fluoroscopic 3D-mapping systems.

Designation by arrows: 1 – circular catheter for recording the electric activity fro the ostium of the pulmonary vein; 2 – catheter for RFA; 3 – balloon catheter for cryoablation positioned in the ostium of the pulmonary vein.

The study FIRE&ICE (2016) comparing the use of radio frequency energy and cryoablation in paroxysmal AF form demonstrate their equal efficiency: about 65% of cases with preservation of the sinus rhythm without administration of anti-arrhythmic drugs for a year after the intervention [101]. In case of AF recurrence, what is associated in most cases with incomplete isolation of the pulmonary veins or delayed recovery of trigger activity conduction from the pulmonary veins to the left atrium, it is possible to perform repeated catheter isolation of the ostia of the pulmonary veins. This increases the total efficiency in preservation of the sinus rhythm up to 80% and more. Isolation of the pulmonary veins is also recommended as the first catheter intervention (radio frequency or cryoablation) for patients with persistent AF form [88].

The efficiency of catheter isolation of the pulmonary veins in patients with persistent and long-standing persistent AF is lower than that in patients with paroxysmal form. Attempts of extended actions in the left atrium (in addition to PV isolation) including linear ablation (modification) of the substrate LA myocardium), zones of so-called CAFÉ (complex atrial fractionated electrograms) in LA, ablation of parasympathetic ganglia, rotors, were made to increase the efficiency of interventions in this patient category. Although the results obtained at some centers, proved to be promising, prospective randomized trials (STARAF, REAFIRM) [102-103] did not confirm the efficiency of such interventions. At present these impacts on the AF "substrate" with the purpose to enhance the efficiency of RFA as the routine practice do not have convincing justification [recommendation class IIb, B/C].

The efficiency of catheter ablation is the highest in subjects aged under 65 years, without signs of organic heart affection, essential hypertension and sleep apnea, having normal or insignificantly enlarged left atrium volume. Catheter ablation may be considered as the first stage of anti-arrhythmic treatment in these patients. The efficiency of intervention in these patient categories may exceed 80%.

The issue on the usefulness of catheter ablation in subjects with asymptomatic course of AF of any form is not solved finally. The question about the intervention in this patient category should be solved taking into account patient's individual risks and preferences [recommendation class IIb, C].

The recommendations on catheter and surgical ablation in AF are summarized in Table 12.

Catheter ablation of AF is associated with the risk of severe and potentially fatal complications including stroke (<1%), cardiac tamponade 1-2%), vessel injures (2-4%), chronic phrenic nerve paresis (1-2%), pulmonary vein stenoses (<1 %), atrio-esophageal fistulas (<0.5%) etc. The rate of lethal outcomes is less than 0.2%. Besides that, asymptomatic embologenic cerebral foci are revealed by MRI in 5-20% of cases. Therefore, catheter ablation of AF should be performed by specialists having sufficient experience in performing such interventions who can diagnose and correct possible complications of the procedure timely and the surgery itself should be performed at a specialized medical center on regularly basis.

Anticoagulant therapy should be administered to all patients in the perioperative period and for not less than 3 months after the intervention even if there are no AF recurrences. A patient should receive the complete and confident information on the benefit, risks and alternative possibilities for treatment of AF before making a decision about the invasive intervention.

The so-called "Labyrinth" surgery including surgical isolation of the pulmonary veins and myocardium fragmentation of both atriums with the help of the so-called technique "Cut and suture" or intraoperative ablation using special bipolar radio frequency

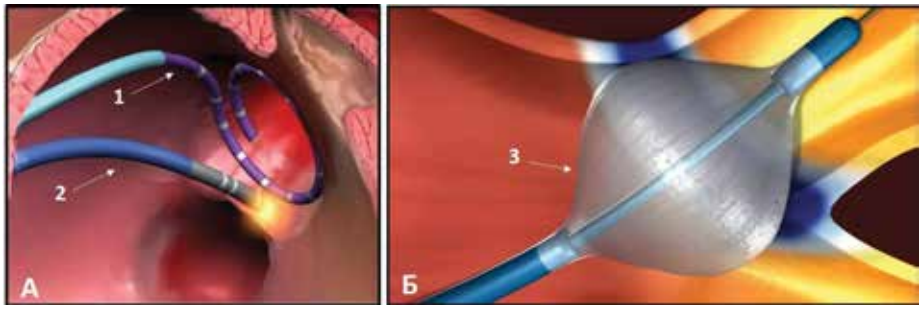

Figure 3. isolation of the ostium of the pulmonary vein by the method of:
A – radio frequency catheter ablation;
B – balloon catheter cryoablation
Designation by arrows: 1 – circular catheter for recording the electric activity fro the ostium of the pulmonary vein; 2 – catheter for RFA; 3 – balloon catheter for cryoablation positioned in the ostium of the pulmonary vein.

Table 12. Recommendations on catheter and surgical ablation in AF

Recommendations on catheter ablation	Class	Level	Reference
Catheter ablation is indicated for patients with symptomatic paroxysmal AF, which is resistant to one or more AAD of class I or III	I	A	88
Catheter ablation is advisable for patients with symptomatic persistent AF, which is resistant to one or more AAD of class I or III	IIa	B	88
Catheter ablation is advisable in patients with heart failure and concomitant AF	IIa	B	96
Catheter ablation can be considered in case of symptomatic long-standing persistent (> 1 year) AF	IIb	C	88
Ablation of "AF substrate" (linear ablation, ablations of CAFE (complex atrial fractionated electrograms), LA ganglia) may be considered as additional stages of catheter ablation	IIb	B	102-103
Catheter ablation may be considered in patients with asymptomatic course of paroxysmal and persistent AF	IIb	C	88
Recommendations on surgical ablation			
Surgical ablation is indicated in case of open-heart surgeries such as mitral valve replacement, coronary artery bypass grafting and others when anti-arrhythmic drugs are not effective	I	B	88
Surgical ablation is advisable in patients with persistent and long-standing persistent AF without other indications for open-heart surgery when previous one or more intracardiac catheter ablations were ineffective	IIa	B	88
Surgical ablation my be considered in patients with paroxysmal AF without other indications for open-heart surgery when previous one or more intracardiac catheter ablations were ineffective	IIб	B	88

Table 13. Recommendations on ablation of atrioventricular connection in patients with atrial fibrillation for HR control

Recommendations	Class	Level	Reference
The usefulness of ablationof AV node forHR control shouldbe considered, if theventricular rhythm rate isnotcontrolled by drugs, it is not possibletoprevent AFrecurrences with the helpof anti-arrythmic drugs or latter cause serious sidee effects and catheter or surgical ablation ofAF is not indicated, proved to be ineffective orits possibility was rejected	IIa	B	105-106
Ablation of AV node is advisable in patients with permanent AFand indications for cardiacresynchroni zationtherapy (heart failure offunctionalclasses III-IV asper NYHA, in spite ofthe optimum drug therapy, with LVEF ≤35% and QRS complex du ration ≥130ms)	IIa	B	104
The usefulness of ablation of AV node shouldbeconsidered in patients who are resistant to resynchronization therapy, in whom highHR with AF doesnot allowto performthe effective bi ventricular stimulation and Amiodaroneis noteffective or is contraindicated	IIa	C	107-108
Ablation of AV node is advisable in patients with anyAF form, dramatically lowered function of LV (EF ≤35%) and severe heart failure (functional-class III -IV as per NYHA). Afterab lation of AVnode the usefulness of biventricular stimulation should be considered	IIa	C	107-108
Ablation of AV node may be considered for HR control in patients with supposed arrhythmogenic cardiomyopathy, impossibility to control the ventricular contraction rate using drugs, if AF triggers/substrate ablation is not indicated, proved to be ineffective or impossible	IIb	C	1-3, 88
The usefulness of ablation of AV node with subsequent resynchronization may be considered in patients with permanent AF, LF EF ≤ 35% and heart failure of functional classes I-II as per NYHA with simultaneous optimum drug therapy for HR control if the drug therapy is insufficiently effective or causes side effects	IIb	C	1-3, 88
Catheter ablation of AV node is not indicated without previous attempts of the drug treatment in order to control HR or catheter ablation of AF with the purpose to maintain the sinus rhythm	III	C	1-3

catheters or special catheters for intracardiac cryothermal exposures may be performed as an additional open-heart intervention in patients with AF referred for surgical treatment of the cardiac pathology (valve replacement, coronary artery bypass grafting etc.) (see Table 12). Surgical methods for treatment of AF allow to perform more reliable rhythm control in patients with persistent and long-standing persistent AF (in 70-90% of cases in the remote future) as compared to traditional catheter interventions. At the same time, intraoperative interventions are associated with the higher risk of complications (up to 6-10%).

8.6.4. Ablation of atrioventricular connection and ventricular stimulation

Ablation of atrioventricular (AV) connection and pacemaker (PM) implantation provide for highly effective control of ventricular contraction rate in patients with AF thereby improving the life quality of these patients but without significant influence on the prognosis. Generation of total or partial (modification of AV conduction) of atrioventricular block is achieved with the help of catheter destruction of the atrioventricular node or His bundle using radio frequency current.

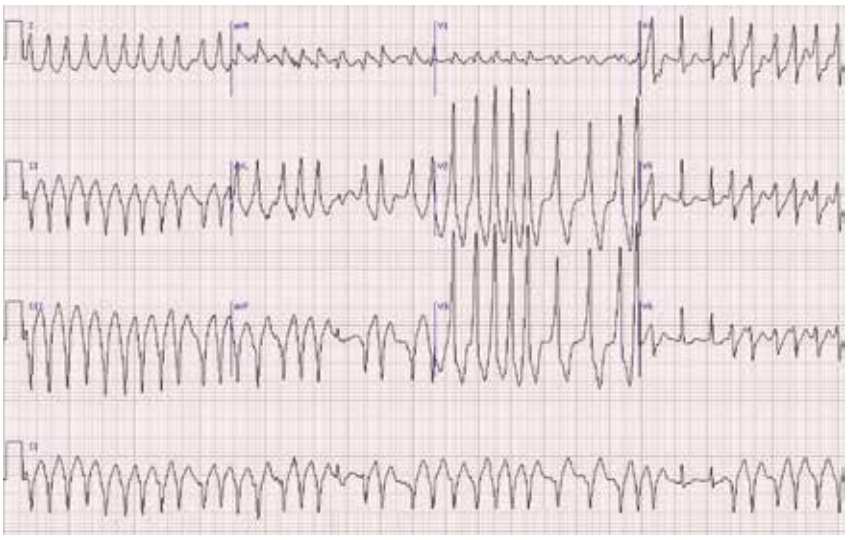

Figure 4. Atrial fibrillation in a patient with WPW syndrome with conduction via Kent bundle. Ventricular contraction rate is 160-250 per minute.

Ablation of AV connection is justified when heart rate control in AF cannot be achieved using the drugs influencing the atrioventricular conduction (see above). Ablation of AV connection may be performed in any variant of clinical AF course but it is carried out the most often in patients with permanent AF form, i.e. in those cases when sinus rhythm preservation is impossible or recognized as not necessary.

The implantable PM should have rate-adaptive function. Single chamber ventricular stimulation in VVIR mode is used for patients with permanent AF form; dual chamber atrial and ventricular stimulation (DDDR) is used in patients with periods of sinus rhythm. Decision o the need to implant a resynchronizing device or automatic cardioverter-defibrillator is made basing on availability of respective additional indications (Table 13).

8.6.5. Atrial fibrillation and flutter in patients with Wolff-Parkinson-White syndrome (WPW)

The presence of WPW syndrome increases the probability of atrial fibrillation and flutter paroxysms. Besides that, availability of an accessory conduction path (ACP) influences critically on the nature of electrocardiographic and clinical signs of these arrhythmias.

Patients with ventricular pre-excitation and AF/AFL have high risk of accelerated conduction via ACP resulting in high ventricular contraction rate (Fig. 4) with potential probability of transformation of AF/AFL to ventricular fibrillation and occurrence of sudden cardiac death (SCD). The rate of SCD in patients with Wolff-Parkinson-White syndrome is from 0.15 to 0.39% over 3-22 years. Catheter ablation of the accessory path is recommended in patients with AF having signs of antegrade conduction via ACP [109-110]. This procedure is safe and effective and may be considered as the strategy for prevention of SCD [I, B] [111-112]. Emergency catheter ablation of ACP is recommended in patients with AF and presence of ACP with history of SCD [109]. Documented AF episodes with short RR interval (<250 ms) are one of risk factors of SCD in patients with WPW syndrome. The usefulness of ablation should be discussed in patients with WPW syndrome and the high risk of AF, in sportsmen going in for competitive sport types and also in workers having dangerous professions such as drivers of public transport, pilots etc.

8.6.6. Surgical and hybrid ablation in AF

Surgical ablation is indicated in patients with symptomatic AF which is resistant to anti-arrhythmic therapy of classes I or III (any course form except for permanent AF) in case if a open-heart surgery is scheduled for a patient (Table 12a): mitral, aortic, tricuspid valve replacement; closing septal defects, coronary artery bypass grafting or their combination [recommendation class I, B]. Surgical ablation in the process of an open-heart surgery may be performed also in patients with any form of AF and without the experience of administration of anti-arrhythmic drugs [recommendation class IIa, B].

Surgical ablation with absence of other indications for an open-heart surgical intervention in patients with persistent and long-standing persistent, symptomatic AF may be recommended in case of inefficiency of AAD, previous unsuccessful attempts (one or more) of catheter ablations [recommendation class IIa, B]. Surgical ablation may be considered with recommendation class IIb, B in patients with paroxysmal symptomatic AF with the same conditions (Table 12a).

The indications and recommendation classes for hybrid thoracoscopic interventions in patients with different AF forms are identical to the indications for surgical interventions listed above [88].

8.6.7. The treatment of patients with atrial flutter (AFL)

The goals for management of patients with AFL are similar to those in the treatment of AF [113]. Basing on the available data, the risk of stroke in patients with atrial flutter is comparable with that in patients with AF [114]. Besides that, many patients with AFL have concomitant AF [115-116].

AFL is referred to atrial tachycardias caused by circulation of the excitation wave in the topographically extensive contour (so-called "macro-re-entry), as a rule, around large anatomic structures in the right or left atrium. Depending on topography of arrhythmia macro-re-entry, two basic AFL types are distinguished:

- **typical or "isthmus-dependent" AFL**,
- **atypical AFL**.

The pulse circulates around the tricuspid valve ring in case of **typical AFL** (Fig. 5). The characteristic feature of this AFL type consists in obligatory repeated passage of the excitation wave via the so-called "cavo-tricuspid isthmus" (CTI), which is the region in the right atrium between the point of flowing of the inferior vena cava in it and the fibrous ring of the tricuspid valve what served as the grounds to call typical AFL as "isthmus-dependent" AFL. The re-entry wave around the tricuspid valve is spreading

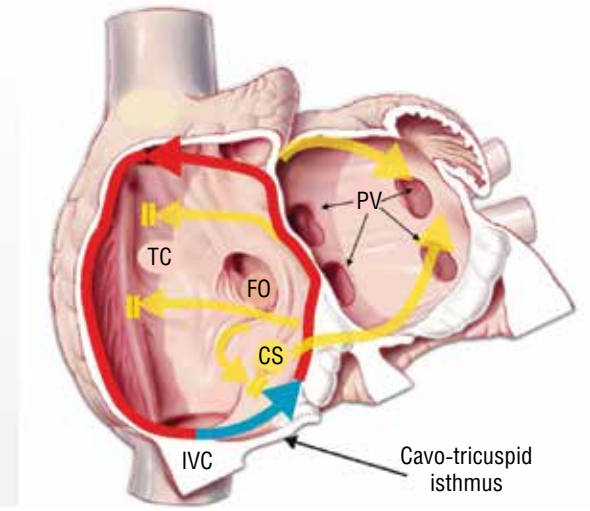

Figure 5. Scheme of typical flutter in the right atrium

Counterclockwise spreading of re-entry wave of typical flutter is designated by red and blue arrows blue arrow = region of slowed conduction in the zone of CTI; yellow arrows = spreading of excitation in the right and left atriums.

Key: SVC = superior vena cava; IVC = inferior vena cava; TC = terminal crest (crista terminalis); FO = foramen ovale; CS = coronary sinus ostium; PV = pulmonary veins.

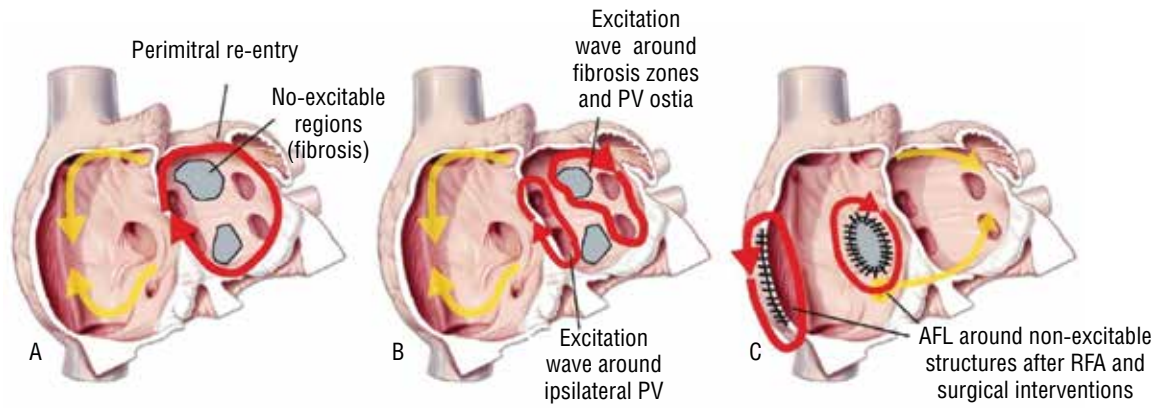

Figure 6. Variants of atypical flutter: A – perimitral flutter, B – flutter around the pulmonary veins; C – so-called "incision flutter" occurring after catheter and surgical interventions.

counterclockwise (when looking from the right ventricle) in the most frequent variant of typical AFL. The excitation wave is spreading in the reversed direction, i.e. clockwise in case of the rarer variant of typical AFL.

All other types of atrial macro-re-entry, the excitation re-entry circuit of which does not include the region of the cavo-tricuspid isthmus, are referred to atypical or "isthmus-independent" AFL. The examples of atypical AFL are electric pulse circulation around the mitral valve, pulmonary veins, fibrosis zones and also around other non-excitable atrial structures including those formed after RFA and open-heart surgical interventions (Fig. 6).

AFL develops practically always with AV- block of degree II and certain, not uncommonly variable ratio of atrioventricular conduction because of high rate of atrial pulsation which exceeds, as a rule, "Wenckebach point" level of the AV node. The variant with permanent ratio of AV-conduction is called the regular AFL form (Fig. 7), and the variant with inconstant ratio is called the irregular AFL form (Fig. 8).

Depending on the ventricular rhythm rate, normosystolic AFL variant (mean rate in the range fro 60 to 100 per minute), bradysystolic AFL variant (rate of less than 60 per minute) and tachysystolic AFL variants (rate of more than 100 per minute) are distinguished.

The development of AFL is a consequence of disturbed processes of electric excitation conduction in the myocardium of the right or left atrium caused, in its turn, by different pathologic processes creating conditions for stable circulation of the electric pulse along a large loop of excitation re-entry (macro-re-entry).

Atrial flutter represents in ECG the regular high-amplitude atrial rhythm with high rate (usually from 250 to 400 per minute) and absence of clear isoelectric line between atrial complexes (F waves) at least in one ECG-lead.

"Saw-tooth" atrial "F"-waves with the maximum amplitude in leads II, III and aVF and also with absence of isoline between them in these or other ECG leads are the leading electrocardiographic signs of typical AFL. It is important to mention that F-waves in the leads II, III and aVF are negative in the frequent variant of pulse circulation around the tricuspid valve in the "counterclockwise" direction (Fig. 8), and they are positive in the same ECG leads in the rare variant of pulse circulation in the "clockwise" direction (see Fig. 7).

Atypical AFL represents usually wave-shaped, rarer saw-tooth atrial activity differing from typical AFL in its ECG-morphology (Fig. 9). Discrete F-waves can be absent at all in standard ECG in some cases of atypical AFL, and transesophageal or intracardiac EPI is required for precise diagnosis of AFL type.

Spontaneous AFL paroxysms are initiated by atrial extrasystoles and when performing EPI, they can be induced and stopped by electric stimuli.

Atrial flutter (similar to atrial fibrillation) is classified in paroxysmal, persistent or permanent forms by its course nature.

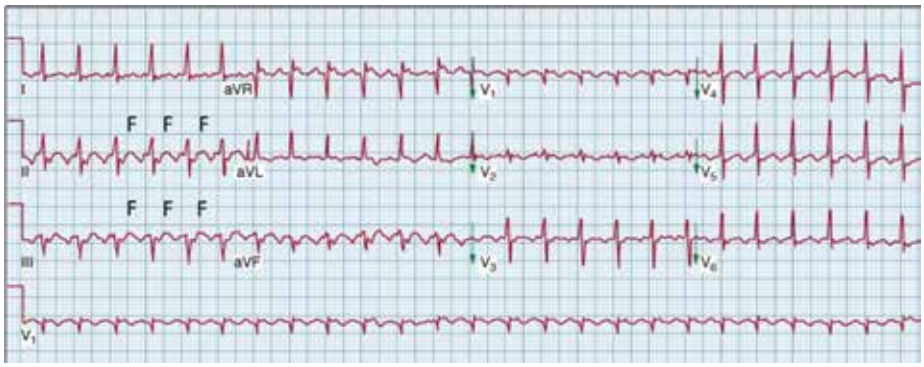

Figure 7. Typical isthmus-dependent AFL ("clockwise" variant) with rate (of F waves) of up to 260 per minute with conduction to the ventricles of 2:1.

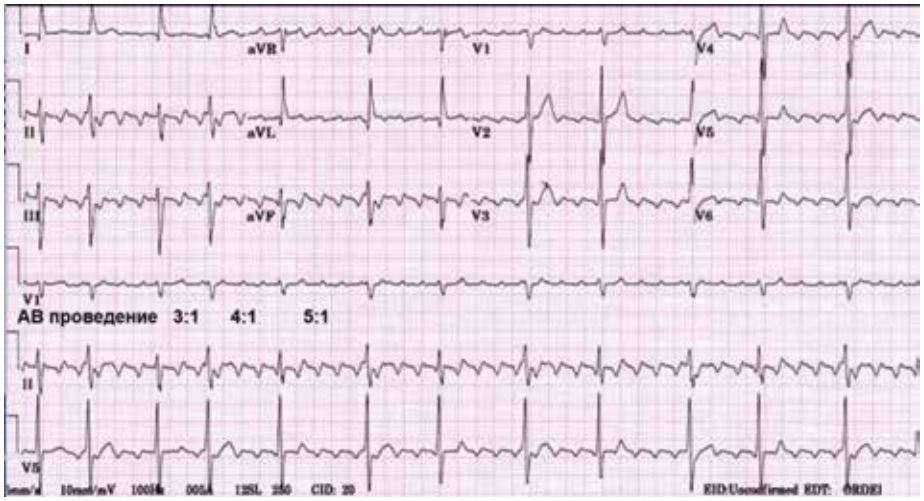

Figure 8. Typical isthmus-dependent AFL with FF wave rate of 250 per minute ("counterclockwise" variant) with variable ratio of atrioventricular conduction from 3:1 to 5:1, i.e. so-called "irregular" AFL form.

Clinical symptoms of AFL depend on ventricular rhythm rate and severity of the underlying cardiac pathology and are similar to those described above for atrial tachycardias.

When AFL (similar to AF) lasts for more than 48 hours patients have increased probability of thrombogenesis in the atriums (first of all, in auricle of the left atrium) what generates a threat of thromboembolic complications. The long therapy with indirect anticoagulants is indicated for these patients if they have concomitant risk factors of thromboembolic complications (as per CHADS2-VASC2 score). Problems concerning prevention of thromboembolic complications in patients with AF and AFL are presented in detail in respective section of these recommendations.

Intravenous administration of Procainamide, Propafenone, Refralon, Sotalol or Amiodarone and also transesophageal atrial electrostimulation are used to stop AFL attacks. Pharmacologic cardioversion using the anti-arrhythmic drug of class III Refralon may be used to recover the sinus rhythm in patients with persistent AFL form (similar to persistent AF). In cases when AFL is associated with pronounced hemodynamic disorders (arterial hypotension, acute coronary insufficiency or heart failure) the emergency electric cardioversion is a method of choice for stopping arrhythmia. Electric cardioversion is also used as a scheduled procedure if attempts of pharmacological cardiac rhythm recovery are ineffective (see above). If an AFL episode lasts for more than 48 h, the sinus rhythm recovery requires prevention of "normalization" thromboembolic complications. The preventive approaches used with this purpose are similar to those used in atrial fibrillation and are considered below.

Beta-adrenergic blockers, Digoxin and their combination and also Verapamil are used to lower the ventricular rhythm rate in tachysystolic AFL variant; these drugs are administered intravenously in acute situations and also per os with the purpose of long-term control of heart rate.

Catheter ablation of the cavo-tricuspid isthmus is a method of choice in the treatment of patients with repeated paroxysms of typical AFL and in persistent typical AFL. This intervention allows to achieve the radical removal of arrhythmia in overwhelming majority (about 95%) of patients with typical atrial flutter. Other supraventricular tachyarrhythmias, the most often paroxysmal atrial fibrillation (AF), are observed in not less than 15-20% of patients after successful ablation of cavo-tricuspid isthmus.

Ablation of cavo-tricuspid isthmus in isthmus-dependent AFL (clockwise or counterclockwise variants) allows to prevent AFL recurrences in 90-95% of patients [117]. This procedure reduces effectively AF recurrences in some patients [118-119]and will help escape unnecessary hospitalizations [120]. Isthmus ablation is a relatively safe and more effective method than anti-arrhythmical drug therapy and it is recommended in recurring course of atrial flutter. Catheter ablation of left atrial macro-re-entry tachycardia is a more complex procedure with lower efficiency and high level of postoperative recurrences.

The recommendations on the treatment of atrial flutter are presented in Table 14.

9. PREVENTION OF STROKE AND SYSTEMIC EMBOLISM IN PATIENTS WITH ATRIAL FIBRILLATION

A very important problem for patients with AF consists in increased risk of ischemic stroke (IS) and systemic thromboembolism (STE), which are the most often of cardioembolic origin what is associated with thrombogenesis in the auricle, rarer in the cavity of the left atrium [121-122]. The mechanisms favoring thrombosis include slowed blood flow, endothelium dysfunction and also

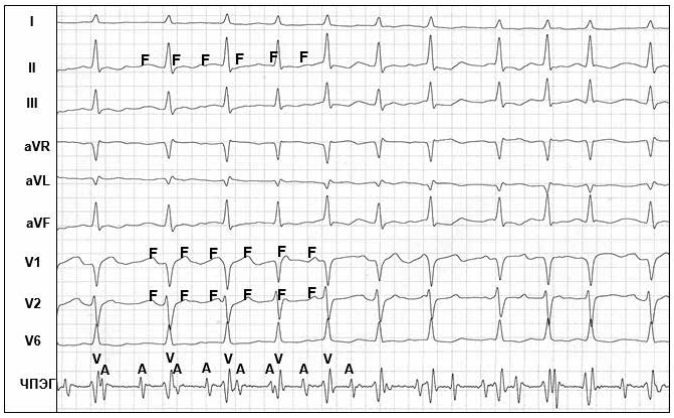

Figure 9. Atypical atrial flutter, irregular form with atrial pulsation rate of FF=300 per minute and conduction to ventricles of 2:1 and 3:1.
Key: TEEG – transesophageal electrogram, A – atrial oscillations, V – ventricular oscillations.

Table 14. Recommendations on prevention and treatment of atrial flutter (AFL)

Recommendations	Class	Level	Reference
Antithrombotic therapy with the same risk profile as that used for AF is recommended for patients with atrial flutter	I	A	117
Ablatio of cavo-tricuspid isthmus in the treatment of typical AFL is recommended for patients with ineffective anti-arrhythmical drug therapy or as the first line of the treatment taking into account patient's preferences	I	B	119
Overdriving atrial stimulation in patients with flutter should be considered as an alterative to electric cardioversion provided that a healthcare facility has the appropriate equipment and experience	IIa	B	117
If AFL was recorded before ablation of AF, it is advisable to perform simultaneous catheter ablation of cavo-tricuspid isthmus and catheter ablation of AF	IIa	C	120

systemic and local activation of the blood coagulation system [123-125]. IS accounts for more than 90% in the structure of all thromboembolic complications in patients with AF.

Stroke is second-the most frequent cause for mortality in the world and about 80% of strokes are of ischemic nature. Cardioembolic stroke has the worst prognosis among ischemic strokes what is associated with the high mortality and stable disablement [126-128].

9.1. Stratification of the risk of stroke and systemic thromboembolism in patients with atrial fibrillation

In order to make a decision on the necessity to prevent stroke in each patient one should assess the risk of this complication. The approaches to stratification of the risk of stroke underwent several changed recently. The CHA_2DS_2-VASc scale is the base for stratification today [1-2]. The age ≥75 years and history of ischemic stroke/transient ischemic attack/systemic embolism are assessed as 2 points, and other risk factors (chronic heart failure/ left ventricular dysfunction, arterial hypertension, age of 65-74 years, diabetes mellitus and presence of a vascular disease: history of myocardial infarction, atherosclerosis of the lower extremity peripheral arteries, aortic atherosclerotic plaque) are estimated as 1 point (Table 15).

The risk of stroke is considered as low in patients with AF receiving not a single point in CHA_2DS_2-VASc scale. These patients do not anticoagulant therapy (ACTh).

On the whole the benefit from administration of the anticoagulant therapy may be expected in case of score 1 in males and score 2 in females. But the studies, which proved the efficiency of anticoagulants (ACG), included patients with the higher risk of stroke, therefore, at present we have strict evidence of efficiency of ACG in case of the total score ≥2 for males and ≥3 for females.

At present the role of biomarkers (highly sensitive troponins T and I and N-terminal precursor of cerebral sodium uretic peptide) is investigated as additional risk factors of stroke among potential risk factors of stroke for male patients having score 1 and female patients having score 2 [2].

Table 15. Risk factors of stroke and systemic embolism in patients with AF and their significance expressed as a score (CHA2DS2-VASc scale)

Risk factors	Score
"C" Chronic heart failure/ left ventricular dysfunction	1
"H" Arterial hypertension	1
"A" Age ≥75 years	2
"D" Diabetes mellitus	1
"S" History of ischemic stroke/transient ischemic attack/systemic embolism	2
"VASc" Vascular disease (history of myocardial infarction, atherosclerosis of the lower extremity peripheral arteries, aortic atherosclerotic plaque)	1
Age of 65-74 years	1
Female sex	1

9.2. Antithrombotic drugs used for prevention of stroke/ thromboembolism in patients with nonvalvular atrial fibrillation

9.2.1. Acetylsalicylic acid

Primary prophylaxis of IS in patients with AF using acetylsalicylic acid (ASS) was assessed in eight large-scale randomized trials [AFASAK-1, BAATAF, SPAF I-III, SPINAF, CAFA], the combined meta-analysis of which [129] showed that ASS lowered relative risk of ischemic stroke, systemic embolism and death by 28% as compared to absence of antithrombotic therapy.

ASS is inferior in its efficiency to peroral anticoagulants both Warfarin and Apixaban, the comparison with which was included in the AVERROES study [130], which showed that Apixaban was more effective than ASS by 55% regarding prevention of the risk of IS/SE with practically comparable rate of massive bleedings. The results of this study served as the last grounds for exclusion of Aspirin from the list of recommended antithrombotic drugs for prevention of IS/SE in patients with nonvalvular AF in the European and Russian recommendations dated 2016-2017 [1-2].

9.2.2. Combination of acetylsalicylic acid and Clopidogrel

The efficiency of double anti-thrombocytic therapy with Clopidogrel and ASS was investigated in the ACTIVE study, branch A of which included comparison of the double antiaggregant therapy with monotherapy with ASS, and in the branch W the combination of Clopigrel and ASS was compared with Warfarin [131-132].

The branch W demonstrated superiority of Warfarin over the double anti-thrombocytic therapy regarding reduced risk of stroke, thromboembolism, myocardial infarction or death because of cardiovascular causes with comparable rate of bleedings including massive ones. The double anti-thrombocytic therapy was more effective by 11% as compared to monotherapy, first of all due to lowered rate of ischemic strokes but the frequency of massive bleedings was considerably higher in the double therapy group. The use of double anti-thrombocytic therapy with the purpose of prevention of stroke and systemic embolism in patients with AF is not recommended in connection with the above data and also taking into account introduction of effective and safe direct peroral anticoagulants (DPACG) [1-2].

9.2.3. Vitamin K antagonists

For a long time vitamin K antagonists (VKA), in particular Warfarin, had been the only peroral anticoagulants which proved their efficiency in prevention of stroke in patients with AF.

The convincing evidences were obtained in six randomized clinical trials [AFASAK-1, SPAF-1, BAATAF, SPINAF, EAFT and CAFA], the combined meta-analysis of which [129] revealed lowered relative risk of stroke (by 2/3) and risk of death (by 1/4) as compared to placebo or administration of ASS.

The mechanism of action of VKA is associated with inhibition of formation of four vitamin K-dependent blood coagulation factors in the liver what results finally in lowered production of thrombin, the key enzyme of blood coagulation.

But availability of the narrow therapeutic window, necessity of monitoring and difficulties in maintaining the international normalized ratio (INR) in the therapeutic range limit the use of Warfarin in the wide clinical practice. Lately the requirements to adequacy of anticoagulation provided by Warfarin became stricter. The TTR parameter reflecting the percentage (%) of INR measurements within the therapeutic range should be not less than 70%.

In 2016 European experts suggested to use SAMe-TT_2R_2 index to prognosticate the possibility to maintain INR in the therapeutic range, see Table 16 [133].

Table 16. SAMe-TT_2R_2 score for assessing prognosis in maintaining TTR >70% in patients receiving VKA

Abbreviation	Parameter		Score
S	Female sex	Female sex	1
A	Age <60	Age < 60 years	1
ME	Medical history	More than two concomitant diseases (arterial hypertension, diabetes mellitus, CHD, atherosclerosis of lower extremity peripheral arteries, CHF, history of IS, hepatic/renal diseases)	1
T	Treatment	Interacting drugs (Amiodarone)	1
T	Tobacco use (doubled)	Smoking	2
R	Race (doubled)	Race (not European)	2

Abbreviations: CHF – chronic heart failure, IS – ischemic stroke

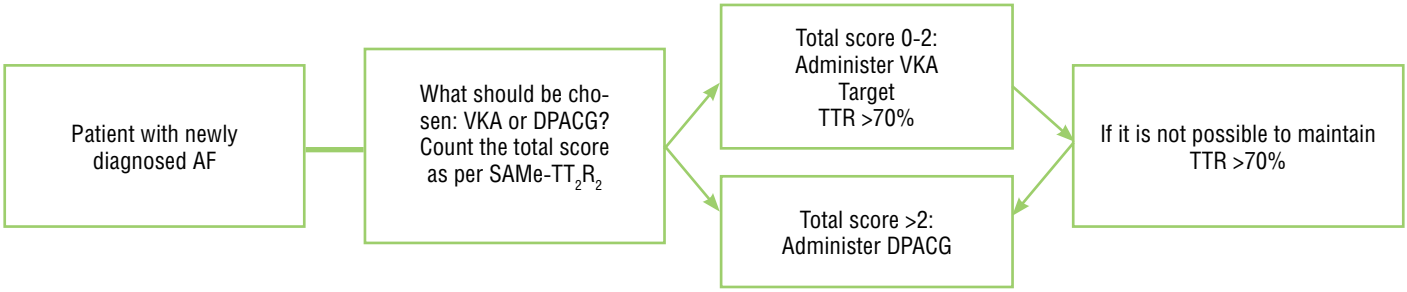

Figure 10. Anticoagulant selection algorithm in a patient with AF having not experience in the anticoagulant therapy [133]

It is suggested to count the total score as per SAMe-TT_2R_2 scale before selecting an anticoagulant for a patient with AF having no experience of their intake. According to the authors, the total score of higher than 2 is associated with high probability of difficulties in selection of INR, and it is worth to administer DPACG to such patients at once (see Fig. 10). It should be noted that this index was not validated in large cohorts and it is finally not unclear how far its wide use is justified.

9.2.3.1. Practical aspects of the therapy with Warfarin

The therapy with Warfarin requires selection of the individual therapeutic dose with reaching the target INR values. The algorithm for selection Warfarin doses is presented in Table 17. Warfarin should be taken once daily at the same point of time. INR should be checked for the first time on day 3-4, then INR should be checked every 2-4 days. Warfarin dose is considered as selected when two close successive INR values are obtained in the target range. INR values measured i different laboratories (including measurements with a portable coagulometer) may differ from each other, and the permissible difference is not more than 20%. It is advisable to use the same laboratory at the stage of dose selection. The lower starting doses (2.5-3.75 mg) are recommended for patients: aged above 75 years, having low body weight, chronic heart/renal failure, in the early postoperative period, with initial hepatic function disorder, in case of concomitant use of Amiodarone. INR may be checked monthly after selection of the individual warfarin dose. The present recommendations allow to extend the period between INR changes in a patient receiving a constant warfarin dose for a long time and having no INR fluctuations to once in 6 weeks.

It is necessary to aim at maintenance of INR in the target range of 2.0-3.0 in all patients including elderly ones. The values of 1.6-2.2 for elderly patients accepted earlier as safe are considered at present as unjustifiably low because of twofold increased risk of stroke at INR < 2.0.

One should aim at lower INR values (2.0-2.5) when Warfarin is administered in combination with antithrombocytic drugs (acetylsalicylic acid or Clopidogrel) or when the therapy is restarted after bleeding.

Such term as “Warfarin average dose” does not exist. Patients differ in the level of the maintenance dose what is associated with several both clinical and genetic factors.

One can speak of true resistance to Warfarin if Warfarin dose ≥20 mg does not result in reaching the target INR values. According to the literature, the number of such cases among patients receiving Warfarin does not exceed 1%. Medical practitioners are often afraid to increase Warfarin dose to more than 7.5 mg what is unjustified because the risk of bleedings does not depend directly on the Warfarin dose but is associated with presence of potential bleeding sources and excessive hypocoagulation. The greater danger regarding hemorrhagic complications exists for patients who need low Warfarin doses (not more than 2.5 mg) for reaching the target INR values what is associated with genetic disturbance of Warfarin metabolism.

9.2.3.2. Drug interactions with Warfarin

Warfarin is the drug which is characterized by multiple drug interactions, therefore, when administering the concomitant therapy, one should prefer the drugs not influencing the anticoagulant effect of Warfarin in order to rule out adverse drug interactions (Table 18.).

But if a drug influencing Warfarin cannot be replaced, it may be administered. In this case one should check INR 3-5 days after

Table 17. Algorithm for selection of warfarin dose (2.5 mg tablets)

The first 2-3 days – 2 tablets (5 mg) once daily at the same point of time		
Day 3-4	INR <1.5	Increase the daily dose by 1/4 tab. INR should be checked in 2 days.
	INR 1.5-2.0	Do not change the daily dose. INR should be checked in 2 days.
	INR ≥ 2.0	Miss 1-2 intakes of Warfarin. Resume the therapy in the dose of 1 tab. when INR is 2.0-2.5. INR should be checked in 1-2 days.
	INR > 3.0	Miss 2 intakes of Warfarin. Resume the therapy in the dose of 1/2 tab. when INR is 2.0-2.5. INR should be checked in 1-2 days.
Day 5-6	INR <1.5	Increase the daily dose by 1/2 tab. INR should be checked in 2 days.
	INR 1.5-2.0	Increase the daily dose by 1/4 tab. INR should be checked in 2 days.
	INR 2.0-2.5	Do not change the daily dose. INR should be checked in 2 days.
	INR 2.5-3.0	Increase the daily dose by 1/4 tab. INR should be checked in 2 days.
	INR > 3.0	Miss 1-2 intakes of Warfarin. Resume the therapy in the dose of 1 tab. when INR is 2.0-2.5. INR should be checked in 1-2 days.
Day 7-8	INR <1.5	Increase the daily dose by 1/2 tab. INR should be checked in 2 days.
	INR 1.5-2.0	Increase the daily dose by 1/4 tab. INR should be checked in 2 days.
	INR 2.0-3.0	Do not change the daily dose. INR should be checked in 2 days.
	INR > 3.0	Miss 1-2 intakes of Warfarin. Resume the therapy when INR is 2.0-2.5. Lower the dose by 1/2 tablet. INR should be checked in 1-2 days.
Later INR should be checked once in 2-3 days using the algorithm of day 7-8.		

Note. In addition to association with several clinical parameters (elderly age, hepatic/renal function disorder, concomitant therapy with Amiodarone), a correlation is revealed between Warfarin dose and ethnicity what allows to consider reduction of the starting dose of Warfarin for these patients fro 5 to 2.5-3.75 mg/day.

Table 18. Drug interactions with Warfarin

Усиливают действие варфарина	Ослабляют действие варфарина
ANTIBIOTICS Penicillins, cephalosporins of generation 2-3, monolactams, Erythromycin Tetracycline, Metronidazole	SEDATIVE DRUGS and ANTICONVULSANTS barbiturates Carbamazepine
CARDIOLOGIC DRUGS Amiodarone, Propafenone, Quinidine Dysopyramide	
NON-STEROIDAL ANTI-INFLAMMATORY DRUGS	CYTOSTATICS Azathioprine Cyclosporine
ANABOLIC STEROIDS	
GASTROENTEROLOGICAL DRUGS Cimetidin Omeprazole	GASTROENTEROLOGICAL DRUGS Sukralfte Antacides
ISONIAZIDE LOVASTATIN	RIFAMPICIN
ALLOPURINOL	
BIOLOGICALLY ACTIVE SUPPLEMENTS Ginkgo Biloba, garlic extract, angelica, papaya extract, vitamin E, Devil's claw (included in the composition of BAS for treatment of arthritis), red sage (included in the composition of Huatuo Pills), Saint-John's wort	BIOLOGICALLY ACTIVE SUPPLEMENTS Ginseng, coenzyme Q10

beginning of the therapy and, if necessary, change Warfarin dose. It is important to have in mind that several biologically active supplements can interact with Warfarin, therefore, it is better to avoid them in order to escape excessive hypocoagulation. The administration of multivitamins is allowed except for the products containing the high vitamin K dose (such drugs are not registered in RF).

One-time use of large quantity of alcohol intensifies the action of warfarin and increases the risk of hemorrhagic complications. Chronic alcohol use vice versa lowers the anticoagulant effect. Therefore, it is better for a patient receiving Warfarin to restrain him(her)self from alcohol use.

9.2.3.3. Alimentary interactions with Warfarin

The intake of products with high content of vitamin K lowers efficiency of Warfarin what is manifested in decrease of INR. The products with high content of vitamin K (300-600 μg/100 g) include dark-green vegetables especially the upper fresh leaves: early cabbage, spinach, mangold leaves, lettuce, Brussel sprouts. The significant quantity of vitamin K is contained in mayonnaise due to vegetable oils (soya, palm oils). The intermediate place regarding vitamin K content is taken by the products containing from 100 to 300 μg of vitamin K per 100 g of the product (haricot, iceberg lettuce, green onion). Dairy products, bakery products, tea, coffee, other vegetables (cucumbers, tomatoes) and fruits contain insignificant quantity of vitamin K (less than 100 μg/100 g of product) and they may be consumed without special limitations. The greater part is vitamin K degrades during the thermal processing. The practice experience evidences that it the most important not to refuse from intake of fresh vegetables but to keep to approximately identical diet over the whole period of the treatment with Warfarin.

9.2.4. Direct peroral anticoagulants

Direct peroral anticoagulants (DPACG) include inhibitors of Xa blood coagulation factor (Rivaroxaban, Apixaban and Edoxaban, which is not approved in RF) and direct thrombin inhibitor Dabigartan.

All DPACG differ from VKA in fastness of reaching (about 2 hours) of the prognosticated anticoagulant effect, similar half-life in blood (about 12 hours), fixed dose and absence of the need to perform the routine laboratory control. ALL DPACG have the renal excretion path from the organism, which is the most pronounced in Dabigatran (up to 80%).

Dabigatran etexilate (hereinafter referred to Dabigatran) was compared with Warfarin in the RE-LY study, Rivaroxaban was compared with Warfarin in the ROCKET-AF study and Apixaban was compared with Warfarin in the ARISTOTLE study and just the results of these studies formed the basis for existing recommendations on antithrombotic therapy in patients with AF [134-136]. While each DPACG has its peculiarities, all three drugs approved in RF demonstrated in the studies of phase 3 common features consisting in the efficiency regarding prevention of stroke and thromboembolism which was at least comparable with that of Warfarin, higher safety in the form of lowered risk of hemorrhagic strokes and in presence of the trend to decreased total mortality. It should be emphasized that the study design provided the comparison with Warfarin and DPACG were not compared between each other, what makes it impossible to state the superiority of any of them.

The results of the studies showed that the efficiency of Dabigatran in the dose of 150 mg and Apixaban regarding lowered risk of stroke and arterial thromboembolism was higher than that of Warfarin, and the efficiency of Dabigatran in the dose of 110 mg and Rivaroxaban did not differ from that of Warfarin. The rate of massive bleedings in patients receiving Dabigatran in the dose of 150 mg and Rivaroxaban was equal to that in patients using Warfarin. The superiority regarding massive bleedings were observed in patients receiving Apixaban and Dabigatran in the dose of 110 mg as compared to Warfarin.

The analysis of the structure of massive bleedings showed that both doses of Dabigatran, Rivaroxaban and Apixaban weree superior to warfarin regarding lowered rate of intracranial bleedings, i.e. this benefit is observed for all DPACG. Nevertheless, patients receiving Dabigatran in the dose of 150 mg twice daily and Rivaroxaban had more gastrointestinal bleedings as compared to Warfarin.

Apixaban proved to be the only one DPACG, which confidently lowered the risk of death because of all reasons as compared to Warfarin. This benefit was associated, most likely, with simultaneous superiority regarding the risk of strokes, SE and massive bleedings as compared to Warfarin.

9.3. ALGORITHM FOR ADMINISTRATION OF PERORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION

Algorithm for administration of anticoagulants in patients with AF is presented in Fig. 11.

Key principles on prevention of stroke in patients with atrial fibrillation

- Peroral anticoagulants are recommended for male patients with total CHA_2DS_2-VASc score ≥2
- Peroral anticoagulants are recommended for female patients with total CHA_2DS_2-VASc score ≥3
- The necessity to administer peroral anticoagulants should be considered in males with CHA_2DS_2-VASc = 1 and females with CHA_2DS_2-VASc = 2 taking into account the patient's individual features and preferences
- One should avoid to administer peroral anticoagulants and antithrombocytic drugs in males and females with AF without risk factors of stroke and systemic embolism
- If VKA are administered, one should aim at thorough control of TTR. If TTR values are low (less than 70%) in spite of good compliance for the treatment, it is necessary to switch to DPACG provided that there are no contraindications (artificial valves)
- DPACG (if there are no contraindications for their administration) should be preferred as compared to VKA in patients with nonvalvular AF having no experience in use of anticoagulants.
- Only vitamin K antagonists (INR ≥2.0-3.0) are recommended for patients with moderate and severe mitral stenosis or mechanical artificial valve
- The monotherapy with antithrombocytic drugs is not recommended for prevention of stroke in patients with AF in spite of available risk of stroke
- The combination of peroral anticoagulants with antithrombocytic drugs increases the risk of bleedings and such combination should be avoided if there are no other indications for its administration.

9.4 RISK ASSESSMENT OF BLEEDINGS

Hemorrhagic complications are the main problem in the long-term therapy with anticoagulants; they can bring to naught all benefits of anticoagulants in patients with AF. Therefore, when making a decision on prevention of thromboembolic complications, it is necessary to assess the ratio between the risks of stroke and massive bleedings, especially intracranial ones, which are the most dangerous complications of ACTh and can cause patient's disablement and even death.

Different scales were suggested to assess the risk of bleedings in patients with AF and the HAS-BLED scale is the most well known of them (Table 19) [1-2].

The HAS-BLED scale was recommended by experts for risk assessment of bleedings in patients with AF before starting the therapy with anticoagulants before 2016. Patients with the score ≥3 were considered as subjects having high risk of bleedings. In 2016, the European experts rejected the HAS-BLED scale to the advantage of assessing the modifiability of risk factors of bleedings what was associated with unjustified non-administration

[a] – including women without other risk factors

[b] – IIaB for women with one additional risk factor of stroke

[c] – IB for patients with mechanical valve or mitral stenosis

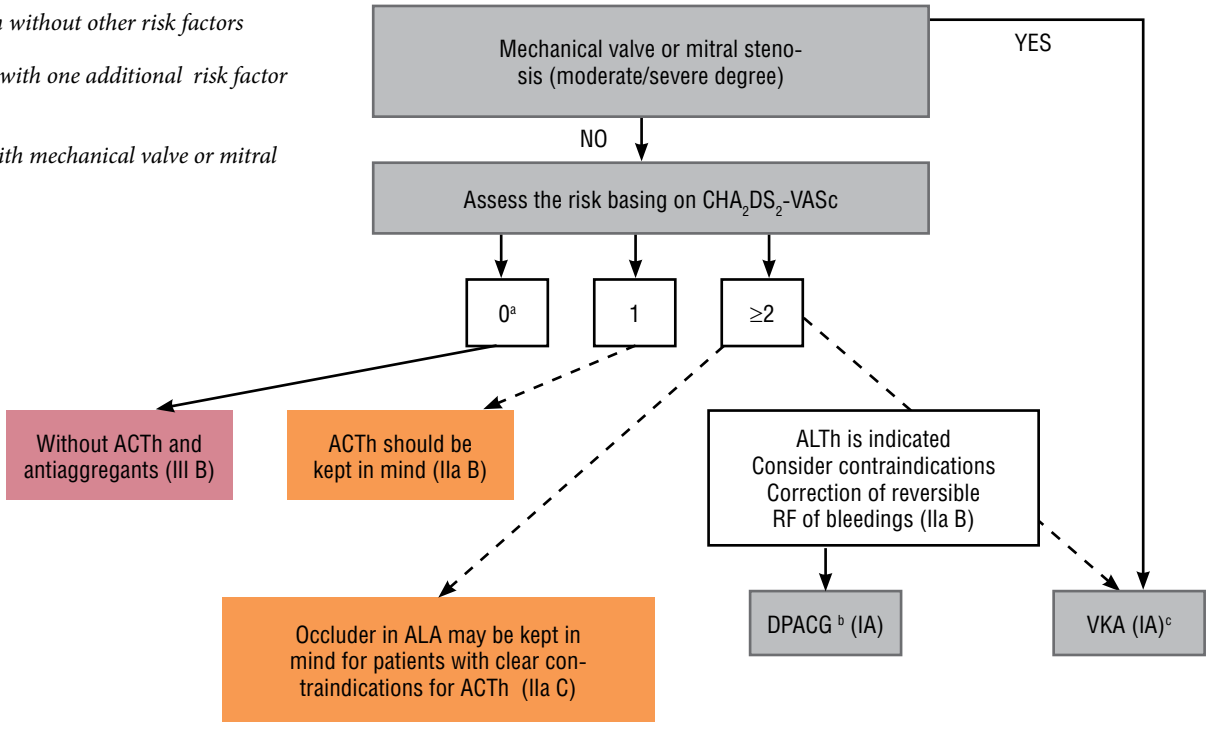

Figure 11. Algorithm for administration of anticoagulants in patients with atrial fibrillation RF – risk factors, AKT – ACTh – anticoagulant therapy, ALA – auricle of left atrium, VKA – vitamin K antagonists, DPACG – direct peroral anticoagulants

Table 19. HAS-BLEED bleeding risk assessment scale

Letter*	Clinical characteristic #	Score
H	Hypertension	1
A	Hepatic or renal function disorder (score 1 each)	1 или 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Age > 65 years	1
D	Drugs or alcohol (score 1 each)	1 или 2
Maximum score – 9		

** First letters pf English terms*
 # "H" – Hypertension – systolic BP >160 mm Hg, "A" – renal or hepatic function disorder: dialysis, kidney transplantation or serum creatinine ≥200 mmol/l; chronic hepatic disease (e.g., cirrhosis) or biochemical signs of serious hepatic disorder (e.g., bilirubin level is at least 2 times higher than the upper limit in combination with increased activity of AST/ALT/alkaline phosphatase (more than 3 times as compared to the upper limit etc.)), "S" – history of stroke; "B" – history of bleeding and/or predisposition to bleeding, e.g., hemorrhagic diathesis, anemia etc., "L" – labile INR, i.e. instable/high INR or <60% of INR measurements are within the target range, "E" – age above 65 years, "D" – drugs/alcohol, i.e. concomitant intake of antithrombocytic, nosteroidal anti-inflammatory drugs (NSAID) or alcohol abuse.

Table 20. Risk factors of bleedings in patients with atrial fibrillation receiving anticoagulants [138]

Modified risk factors
Arterial hypertension (especially if SBP >160 mm Hg)
Labile INR or time in therapeutic range of INR is less than 60% (for patients receiving vitamin K antagonists (VKA))
Concomitant use of drugs increasing the risk of bleeding (antiaggregants or NSAID)
Alcohol abuse (≥8 portions per week)
Partially modified risk factors
Anemia
Disturbed renal function
Disturbed hepatic function
Decreased thrombocyte number or their disturbed function
Unmodified risk factors
Age (> 65 years), (≥75 years)*
History of massive bleeding
History of stroke
Renal pathology requiring dialysis or kidney transplantation
Hepatic cirrhosis
Malignant neoplasm
Genetic factors
Biomarkers – risk factors of bleedings
Highly sensitive troponin
Growth differentiation factor 15
Serum creatinine level/calculated creatinine clearance

Abbreviations: BP – blood pressure, NSAID – nonsteroidal anti-inflammatory drugs, TTR – time in therapeutic range, GDF-15 – growth differentiation factor 15.

of anticoagulants in the routine clinical practice [137]. The main task for a physician before administration of ACTh is to correct the modified risk factors and select the most safe anticoagulant if there are unmodified factors (Table 20).

The potential bleeding sources should be assessed before administration of any antithrombotic drug. Special attention should be paid to presence of erosive-ulcerative lesion in the gastrointestinal tract (GIT), urolithiasis and inflammatory diseases of the urogenital system, chronic hemorrhoids, malignant neoplasms, uterine myoma, aneurysm of aorta and its branches including intracranial arteries etc. (the investigation plan before prescription of ACTh is presented in Table 21). A decision on

Table 21. Investigation plan for a patient before administration of the anticoagulant therapy

Obligatory investigations	Additional investigations
1. Complete blood count (hemoglobin, erythrocytes, thrombocytes)	1. Esophagogastroduodenoscopy, if necessary, colonoscopy
2. Biochemical blood analysis (hepatic specific enzymes, creatinine, urea, total protein).	2. Ultrasound investigation of the kidneys if erythrocyturia is revealed
3. Coagulogram (prothrombin with calculation of INR, APTT)	3. Computed tomography and/or magnet resonance imaging for patients with recent history of stroke and also with pronounced residual neurologic deficit in order to rule out hemorrhagic stroke and vascular malformations
4. Fecal occult blood test (as screening for blood loss through GIT)	4. Examination by a gynecologist
5. General urine analysis (to rule out erythrocyturia)	5. Examination by an ophthalmologist (to rule out hemorrhagic complications on the eye retina)

GIT – gastrointestinal tract, INR – international normalized ratio, APTT – activated partial thromboplastin time

administration of antithrombotic drugs in difficult cases should be made by a board of doctors of concerned specialties.

How to lower the risk of bleedings in patients receiving peroral anticoagulants?

1. Obligatory investigation for verification of potential bleeding sources, ruling out of anemia and assessment of hepatic and renal function.
2. The monotherapy with anticoagulants is sufficient in most cases in patients with AF and stable CHD.
3. DPACG demonstrated lower rate of hemorrhagic complications as compared to Warfarin in patients with AF, therefore, the administration of DPACG should be preferred over Warfarin in patients having no experience of the treatment with peroral anticoagulants.
4. For patients with the history of bleeding from the upper GIT, erosive-ulcerative lesion in these region, it is advisable to use Apixaban or Warfarin but not Rivaroxaban or Dabigatran in the dose of 150 mg.
5. The renal function should be assessed at baseline and over time for all patients receiving anticoagulants. The experts recommend to use Cockcroft-Gault formula to assess the renal function. Basing on the creatinine clearance value one should select the optimum DPACG or correct the dose.
6. If the creatine clearance is less than 15 ml/mn, DPACG are contraindicated, Warfarin is allowed but its use is also difficult because of extremely high risk of bleeding in this patient category. Dabigatran is contraindicated if creatine clearance is less than 30 ml/min.
7. The glomerular filtration rate (GFR) should be regularly checked not less than annually in all patients receiving peroral anticoagulants and not less than once per six months for patients aged ≥75 years. For patients with GFR <60 ml/min it is recommended to use a formula to calculate the frequency of renal function check: once in N months where N = creatinine clearance/10. The additional analyses should be planned if any intercurrent disease could influence the renal function.
8. One should aim at target INR values in patients receiving VKA. The features of alimentary and pharmacologic Warfarin interactions should be explained to patients. If it is not possible to maintain TTR (time in therapeutic rage of INR) ≥70% patients should be switched to DPACG.
9. The first control visit of a patient starting to use DPACG to a doctor should be in 1 month in order to assess the drug tolerance, risk of bleedings, make a decision on additional analyses and, if necessary, correct the drug dose. The follow-up is carried out with the interval of 1-6 months taking into account the age, renal function, risk of bleedings and concomitant diseases.
10. When administering DPACG one should aim at prescription of the full drug dose (Dabigatran – 150 x twice daily, Rivaroxaban – 20 mg /day, Apixaban – 5 mg x twice daily) restricting the use of the lowered dose by special indications: Dabigatran is administered in the dose of 110 mg twice daily in case of the age ≥80 years, concomitant use of Verapamil, increased risk of gastrointestinal bleedings and in patients with GFR <50 ml/min with increased risk of bleedings: Rivoxaban is administered in the dose of 15 mg daily if GFR ≤50 ml/min, Apixaban is prescribed in the dose of 2.5 mg twice daily provided there are at least two signs out of three, i.e. age ≥80 years, weight ≤ 60 kg or GFR of 15-29 ml/min).
11. BP should be strictly checked in patients receiving the antithrombotic therapy.
12. The danger of alcohol abuse should be actively explained to patients.
13. Intramuscular injections are contraindicated if anticoagulants are used.
14. The concomitant use of glucocorticoids and nonsteroidal anti-inflammatory drugs should be minimized (the use of Naproxen/Piroxicam is associated with high risk of bleedings and Paracetamol and Ibuprofen have the lowest ulcerogenic effect).
15. Selection of the correct perioperative tactics avoiding unmotivated change of anticoagulants including as "bridging therapy" (see chapter "Anticoagulant therapy and invasive interventions").

9.5. Non-drug methods for preventive of ischemic stroke in patients with atrial fibrillation

The auricle of the left atrium (ALA) is the most frequent source of cardioembolism (up to 91% of cases in patients with nonvalvular AF, 57% in patients with valvular form of AF) [139] what is the grounds for development of ever more new invasive interventions aimed at exclusion of ALA from the blood flow. There are surgical, endovascular and hybrid methods of ALA isolation.

9.5.1. Surgical methods for ALA isolation

Different surgical techniques of ALA isolation have been developed by now. All they include closing the ostium of ALA with

or without ablation of ALA itself. The ostium of ALA is closed by endocardial or epicardial method including the use of additional devices [140]. But al these procedures have several restrictions, first of all, it is possible incomplete isolation of ALA. The residual junction between the auricle and LA cavity is preserved on average in one third of patients. The formed junction preserves the risk of thromboembolism at least at the former level or even higher. ALA amputation is considered the more reliable method but this intervention may be complicated with heart tamponade and myocardial ischemia. The enhanced efficiency of ALA isolation is achieved by introduction in practice of special devices, e.g. ArtiClip atraumatic clips (Atricure, WestChester, OH, USA) which can be used both during open-heart surgical interventions and minimally invasive thoracoscopic interventions [141]. Surgical staplers (e.g., EndoGIA, Medtronic, USA) can be use also for ALA resection [142]. They are used the most often in the combined thoracoscopic intervention, i.e. isolation of pulmonary veins ad ALA resection.

At present evidences of benefits of surgical ALA isolation regarding thrombotic complications in patients with AF are extremely limited [143]. Moreover, the data is available that such intervention can even increase the risk of postoperative AF (without increased risk of TEC) [144].

Thus, the possibility of surgical ALA isolation may be considered in patients with AF undergoing a cardiosurgical intervention [2]. The selected method should provide for the maximum full ALA isolation without formation of the residual junction.

9.5.2. Endovascular methods for ALA isolation

This intervention type includes implantation of special device into ALA: this device is the occluder closing the junction between LA and ALA. At present two types of devices are available in RF for commercial use: **Watchman** (BostonScientific, Natwick, MA, USA) and **AmplatzerCardiacPlug** in **Amulet** modification (Abbot, USA), Plymouth, MA, USA). It should be noted that the results of RCT assessing the efficiency and safety of occluder implantation as compared to Warfarin (PROTECT-AF, PREVAIL) are available only for Watchman device [145].

Occluder implantation may be considered provided that there are contraindications for the long-term anticoagulant therapy in patients with AF and high risk of thromboembolic complications [2].

Selection and preliminary investigation of patients

TE-EchoCG should be performed in order to rule out thrombosis and also assess more precisely the structure and dimensions of ALA before occluder implantation. ALA thrombosis is a contraindication for occlude implantation. TE-Echo-CG assesses also such parameters as orientation and length of ALA, shape and size of ALA ostium, number of lobes and peculiarities of pectineal muscles structure. Tridimensional TE-EchoCG is performed in some situations provided that the appropriate equipment is available. The standard protocol of the preoperative investigation at many clinics includes also multi-slice spiral computed tomography (MSCT) with contrast enhancement. Recently the studies appeared on the advisability of 3D-MSCT with printing the ALA cast using the 3D-printer.

The ALA structure predetermines the possibility to implant occluder and the potential success of this procedure. At present several variants of ALA structure are described basing on the CT-picture; the most widespread variants are the following: 'hen's wing' (48%), 'cactus' (30%), 'wind sock' (19%) and 'broccoli' (or 'cauliflower') [147]. The latter structure variant is associated with the maximum difficulties in occlude placement.

The size of the occluding device is determined by the maximum diameter of ALA ostium. The device diameter should be larger by 10-20% than the diameter of ALA ostium what provides for the sufficient compression on the chamber walls and, respectively, greater occluder stability.

Implantation of occluding device

Occluders are implanted in settings of X-ray operating room under control of roentgenoscopy and TE-EchoCG (or intracardiac Echo-CG). Heparin (the starting dose is 100 U/kg, the target

Table 22. Indications for implantation of devices occluding the auricle of the left atrium in patients with AF (according to [146] with modifications)

Impossibility of long-term anticoagulant therapy (absolute or relative contraindications)	
High risk of bleedings	
History of massive bleeding the causes of which cannot be removed (with simultaneous anticoagulant therapy or without it)	For example: • intracranial hemorrhages • bleedings in the vital organs (spinal cord, pericardial cavity, eyeball etc.) • other massive bleedings (the most often gastrointestinal bleedings)
High risk of bleedings because of presence of concomitant diseases	For example: • diffuse amyloid angiopathy of intracranial arteries • intestinal angiodysplasia • severe renal failure/ hemodialysis • several blood diseases characterized by increased risk of bleeding
Impossibility to administer peroral anticoagulants because of other reasons (not associated with increased risk of bleedings)	
	For example: • drug intolerance • documented low compliance for the treatment in spite of all necessary doctor's explanations • documented INR variability in a patient who can take only VKA (in spite of correction of potential causes for INR fluctuation) • professions of high risk associated with great probability of traumatization • patient's choice

activated coagulation time is >250 s) is administered during the procedure after puncture of the interatrial septum; if necessary, the activated coagulation time should be checked every 30 minutes. The administration of heparin is not indicated after implantation. The data is available on successful use of Bivalirudin as the anticoagulant support for occlude implantation.

The criteria of technical success of occluder implantation: 1) ALA isolation; 2) absence of complications associated with the device (embolization by the device, erosion in the point where the device adjoins to the tissue, clinically significant stenosis of adjoining cardiac structures, i.e. mitral valve, pulmonary veins, pulmonary artery, circumflex coronary artery, involvement of other cardiac structures in case of device migration, device thrombosis, device destruction, device infection with endocarditis etc.); 3) absence of marginal blood flow of more than 5 mm according to findings of color flow mode during TE-EchoCG [146].

Patient management after occluder implantation

The intensive follow-up is indicated for a patient after the intervention: it is necessary to assess the neurologic status, check the local status taking into account the possible formation of hematoma or bleeding from the puncture site of the femoral vein. The pericardial cavity condition is assessed just before the transfer of a patient from the X-ray operating room. Antibiotic prophylaxis should be administered in accordance with the local protocol. The standard prevention of bacterial endocarditis is indicated for subsequent 6 months.

The occluder is a foreign body on the surface of which thrombi can be formed. A patient should receive the antithrombotic treatment till the time of endothelization.

Patients should take Warfarin (INR 2.0-3.0) and Aspirin in the dose of 75 mg/day for at least 45 after the procedure for implantation of the WATCHMAN device (the duration is determined by the period of endothelization of the device surface). The occluder positioning is checked with the help of TE-EchoCG in 45 days. If the device is positioned optimally (full occlusion of ALA ostium, the marginal flow is not more than 5 mm) and there are no thrombotic masses on the occlude surface, Warfarin may be withdrawn. Clopidogrel in the dose of 75 mg should be administered in combination with Aspirin for the period of up to 6 months after implantation, then Aspirin should be prescribed for indefinite period of time. If the device is positioned inadequately, the treatment with Warfarin should be continued to reduction of the flow to less than 5 mm [148]. Thus, if the standard protocol is followed, the Watchman device is intended for patients who can receive Warfarin for a short period.

The combination of Aspirin in the dose of 75 mg and Clopidogrel in the dose of 75 mg is administered for a period from 3 to 6 months after implantation of the ACP Amulet device with subsequent switching to the monotherapy with antiaggregant [147].

Taking into account that the devices occluding ALA are intended for patients having contraindications to anticoagulants, these drugs are often not administered, the period of double antiaggregant therapy is shortened, the treatment is restricted to monotherapy with antithrombocytic drugs or the antithrombotic treatment even is not administered at all in the actual clinical practice after occlude implantation [150]. DPACG are administered in some centers as the anticoagulant support [151]. All these approaches have not been studied yet within the limits of randomized trials what requires the development of local protocols for each clinic.

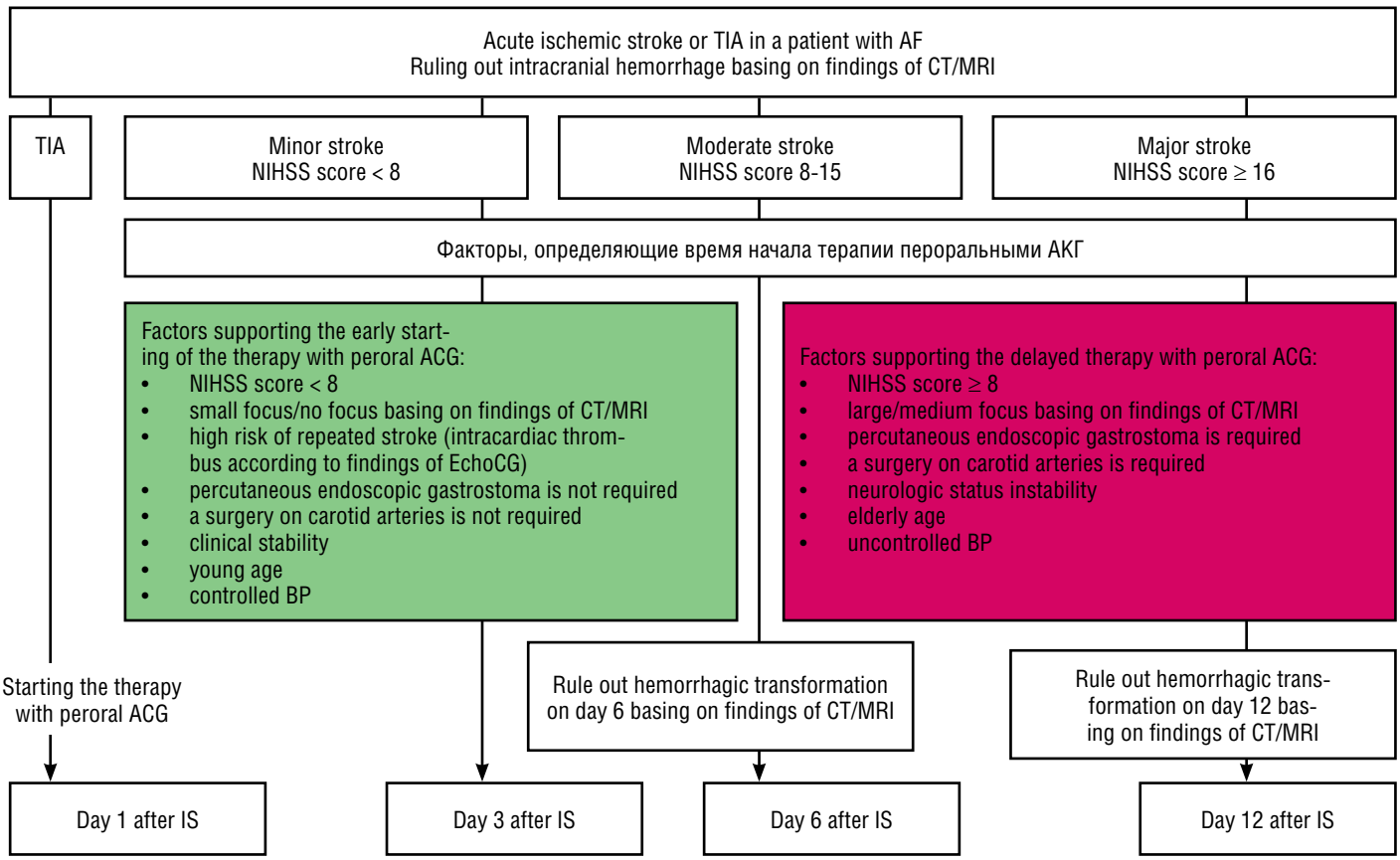

Figure 12. Algorithm for starting or resuming the therapy with peroral anticoagulants in patients with AF and acute ischemic stroke or transient ischemic attack. *Abbreviations and symbols: NIHSS – National Institute of Health Stroke Scale, ACG – anticoagulants, CT – computed tomography, MRI – magnet resonance imaging, BP – blood pressure, IS – ischemic stroke, TIA – transient ischemic attack, AF – atrial fibrillation*

The control TE-EchoCG is performed 45 days after the time of implantation irrespective of the device type in order to assess the device position, degree of ALA occlusion, magnitude of the marginal flow, presence of a thrombus on the device surface. In case of questionable results of TE-EChoCG it is possible to perform MSCT with contrast enhancement, which allows to assess more precisely the magnitude of the marginal flow and also estimate the degree of device endothelization to solve the problem of the optimum time for withdrawal of anticoagulants. If a thrombus or the intense marginal flow are revealed, it is advisable to extend the antithrombotic therapy. The probability of a thrombus on the occlude surface indicates that TE-EchoCG should be performed in such patients before cardioversion.

9.6. Special cases of antithrombotic therapy in patients with atrial fibrillation

9.6.1. Antithrombotic therapy in patients with AF and ischemic stroke or transient ischemic attack

The experience in the use of anticoagulants in patients with AF during the first days of ischemic stroke is not rich. Making a decision on the time of starting/resuming the therapy with peroral anticoagulants is based on the assessment of the cerebral focus size and severity of neurologic deficit (consciousness level, motor activity, sensitivity, speech etc.) determined by the total score as per the National Institute of Health Stroke Scale [1-2]. In accordance with such viewpoint, experts recommend not to interrupt the use of anticoagulants in patients with TIA and start/resume ACTh in patients with confirmed IS within the period of 3-12 days depending on stability of the neurologic status and findings of neurovisualization. Experts emphasize the necessity of neurovisualization over time to rule out hemorrhagic transformation in patients with severe and moderate strokes (see Fig. 12).

One should have in mind the possibility to administer Aspirin to patients having contraindication for prescription of anticoagulants in the early period of ischemic stroke. If a patient receiving anticoagulants develops stroke, his (her) compliance for the therapy with anticoagulants at the time of stroke onset should be assessed, and if stroke developed in spite of adequate therapy with the anticoagulant it should be replaced. According to experts, the administration of DP ACG is preferred as compared to VKA or Aspirin in patients suffering from AF with history of ischemic stroke.

9.6.2. Resumption of the therapy with anticoagulants in a patient suffering from AD with history of intracranial bleeding

There are no specially designed studies aimed at answering the question on whether it is possible to resume the anticoagulant therapy after intracranial bleeding and, if possible, when this may be done. Patients with history of intracranial bleeding were excluded from randomized clinical trials comparing Warfarin and DPACG.

According to expert's opinion, reflected in the latest European recommendations on the treatment of patients with AF [1-2], it is possible to resume ACTh in a patient with AF in 4-8 weeks after the intracranial hemorrhage provided that there is an established cause for bleeding or when the risk factor causing bleeding can be treated and controlled. A decision on resumption of the anticoagulant therapy should be made by a multidisciplinary team consisting of neurologists, cardiologists, neurosurgeons and specialists in neurovisualization. Besides that, a patient and members of his(her) family should be informed about the risk and benefit of resuming the therapy with anticoagulants. When selecting the anticoagulant, it is rational to choose a drug having the minimum risk of bleedings. VKA may be preferred as compared to DPACG in patients with nonvalvular AF with history of intracranial hemorrhage. When resuming the anticoagulant therapy in such patients, if possible, one should avoid combinations with antiaggregants; INR should be maintained within the range 2-2.5 for patients receiving VKA; the time in therapeutic range of INR should be not less than 65-70%; DPACG should be administered in the minimum doses which are effective in prevention of stroke and systemic embolism. The blood pressure level should be thoroughly checked, especially in patients with hemorrhage localization which is typical for hypertonic angiopathy (basal ganglia, thalamus, brain stem). Such patients also should exclude alcohol use which increases significantly the risk of intracranial hemorrhage.

The algorithm for making a decision to resume the therapy with anticoagulants after intracranial bleeding recommended by the European experts in 2016 is presented in Fig. 13.

9.6.3. Antithrombotic therapy in patients suffering from AF with history of acute coronary syndrome or those who underwent percutaneous coronary interventions

AF is closely associated with coronary heart disease (CHD). The analysis of the REACH register, which included more than 60,000 patients with stable signs of atherothrombosis, showed that the rate of AF in this patient category was 10.7% [152]. The double antithrombocytic therapy including Aspirin and thrombocyte P2Y12 receptor blocker is administered in order to lower the risk of thrombotic complications after PCI including stent thrombosis. The antithrombocytic therapy is insufficient to lower the risk of stroke in patients with AF what is the grounds for administration of the triple antithrombotic therapy to a patient with AF with history of ACS or scheduled PCI. The results of numerous meta-analyses combining patients with AF showed that the triple antithrombotic therapy consisting of acetylsalicylic acid, Clopidogrel and peroral anticoagulants was 2-4 times more dangerous than the double antithrombotic therapy regarding the risk of major and fatal bleedings [153-155]. For patients receiving the multicomponent antithrombotic therapy, every tenth bleeding may be fatal; among them intracranial and gastrointestinal hemorrhages are observed nearly with equal rate.

Prasugrel and Ticagrelor included in the triple therapy have not been studied; it is suggested that more powerful antiaggregants are potentially more dangerous regarding the risk of bleedings and, therefore, only Clopidogrel is recommended as a component in the triple therapy [156].

The VKA dose included in the triple antithrombotic therapy should be minimum effective (INR 2.0-2.5) and TTR (time in therapeutic range of INR) should be not less than 65-70%.

Only Warfarin was considered as an anticoagulant drug in the triple antithrombotic therapy before 2014. The use of DPACG in patients with AF who underwent scheduled TCCI was officially approved by European experts from 2014, and the results of randomized trials (PIONEER AF-PCI, REDUAL-PCI, AUGUSTUS) assessing safety of different strategies for the use of DPACG included in the multicomponent antithrombotic therapy are being published starting from 2016 [157-159]. When using DPACG as a component of triple antithrombotic therapy, one should select the

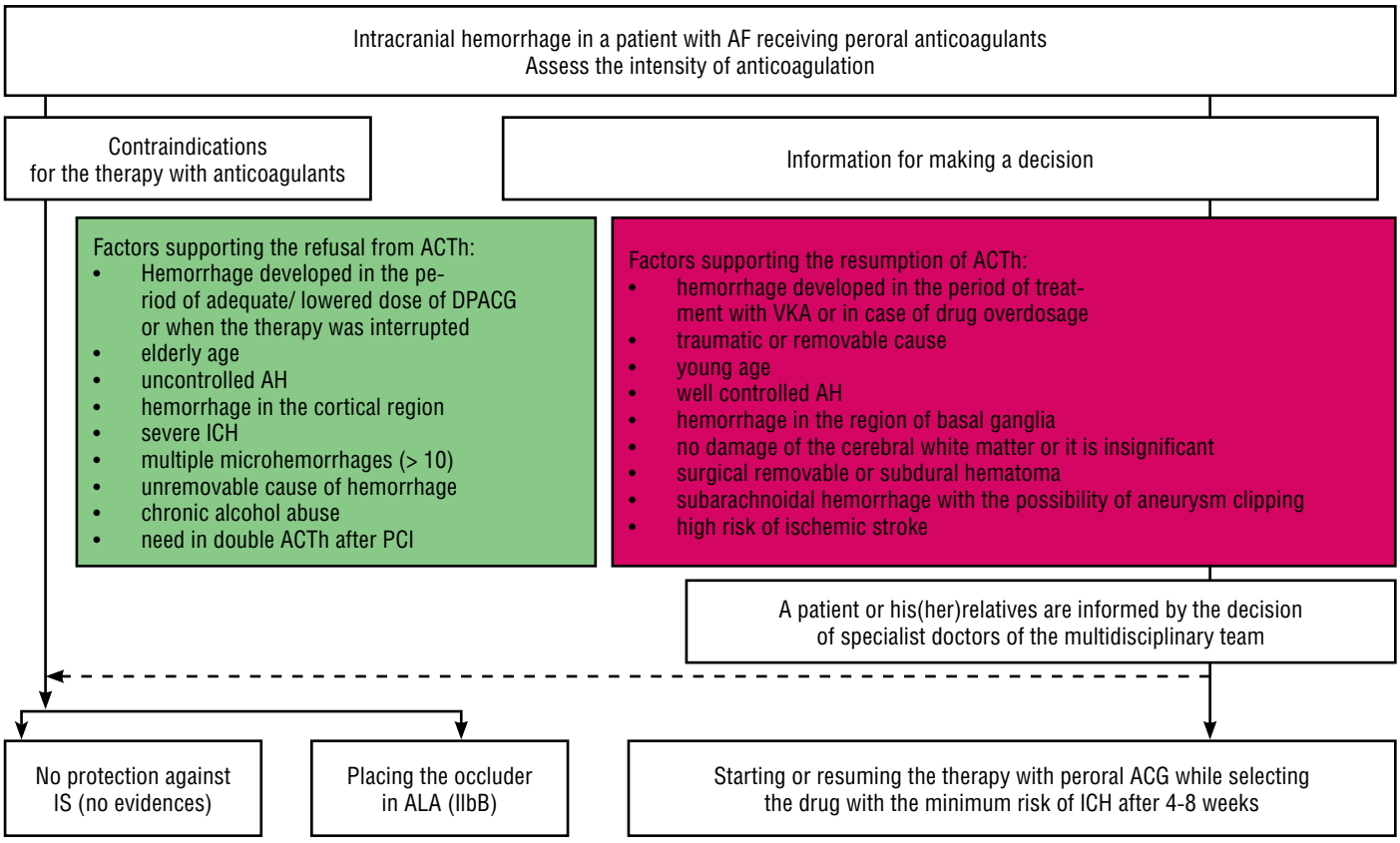

Figure 13. Algorithm for making a decision on the possibility to resume the anticoagulant therapy in a patient with the history of intracranial hemorrhage. *Abbreviations: ACTh – anticoagulant therapy, ACG – anticoagulants, AH – arterial hypertension, VKA – vitamin K antagonists, ICH – intracranial hemorrhage, PCI – percutaneous coronary intervention, DPACG – direct peroral anticoagulants, IS – ischemic stroke, ALA – auricle of the left atrium, AF – atrial fibrillation*

minimum doses, which proved to be effective in randomized trials serving as the grounds for their use. Dabigatran should be used in the dose of 110 mg twice daily for elderly patients, subjects receiving glycoprotein P inhibitors (e.g., Verapamil) and also patients with the high risk of bleedings; Rivaroxaban should be used in the dose of 15 mg, especially in patients with the high risk of bleedings or creatinine clearance of 30-49 ml/min; Apixaban is administered in the dose of 5 mg twice daily and it is used in the dose of 2.5 mg twice daily for subjects having at least two of three signs listed below (age ≥80 years, body weight ≤60 kg, creatinine clearance ≥1.5 mg/dl (133 μmol/1)) [156-157].

It is necessary to emphasize that in spite of the fact that design of the PIONEER AF-PCI study [158] included comparison of the triple therapy (Warfarin + Clopidogrel + ASS) with double therapy (Rivaroxaban in the dose of 15 mg + Clopidogrel), prescription of the double antithrombotic therapy to all patients with AF immediately after PCI is not supported by the current recommendations. Experts allow the use of immediate double therapy (the combination of peroral anticoagulant and Clopigrel only in cases of very high risk of bleeding the example of which is the history of major bleeding).

The opinion on the optimum duration of the triple antithrombotic therapy (TAT) after a scheduled PCI in a patient with AF underwent several considerable changes recently and still remains a subject for discussion. The factors promoting the extension of TAT include the use drug-coated stents of the first generation and presence of the risk factors of thrombotic complications (such as stenting of the left coronary artery trunk or the proximal segment of the anterior descending artery, bifurcation stenting, history of myocardial infarction or stent thrombosis, high SYNTAX score). The high risk of bleedings and low atherothrombotic risk (assessed also using the REACH or SYNTAX scales) support shortening of TAT duration. According to the joint experts' opinion presented in the collegial document dated 2018, the TAT duration may be from 1 to 6 months and the minimum duration may be restricted to hospitalization period with administration of the double antithrombotic therapy (combination of the full DPACG dose and Clopidogrel) immediately after patient's discharge from the hospital [156]. Aspirin and Clopidogrel are administered after obtaining the findings of CAG, just before PCI irrespective of the chosen strategy. When administering the combined antithrombotic therapy, it is reasonable to prescribe proton pump inhibitors with the preventive purpose.

Algorithm for selection of the strategy for the multicomponent antithrombotic therapy in patients with atrial fibrillation after ACS or those who underwent scheduled PCI is presented in Fig. 14 and 15.

9.7. Anticoagulant therapy and invasive interventions

The modern viewpoints regarding the perioperative tactics underwent several changes.

Minor invasive interventions (teeth extraction, procedures on canals of dental root, minor dermatologic surgeries, cataract removal), many invasive cardiologic interventions (coronary angiography and percutaneous coronary intervention with radial access, pacemaker implantation) can be carried out not withdrawing peroral anticoagulants and the use of local hemostatic agents. In this case, one should consider the possibility of temporary withdrawal of Warfarin for the period of up to 48 hours

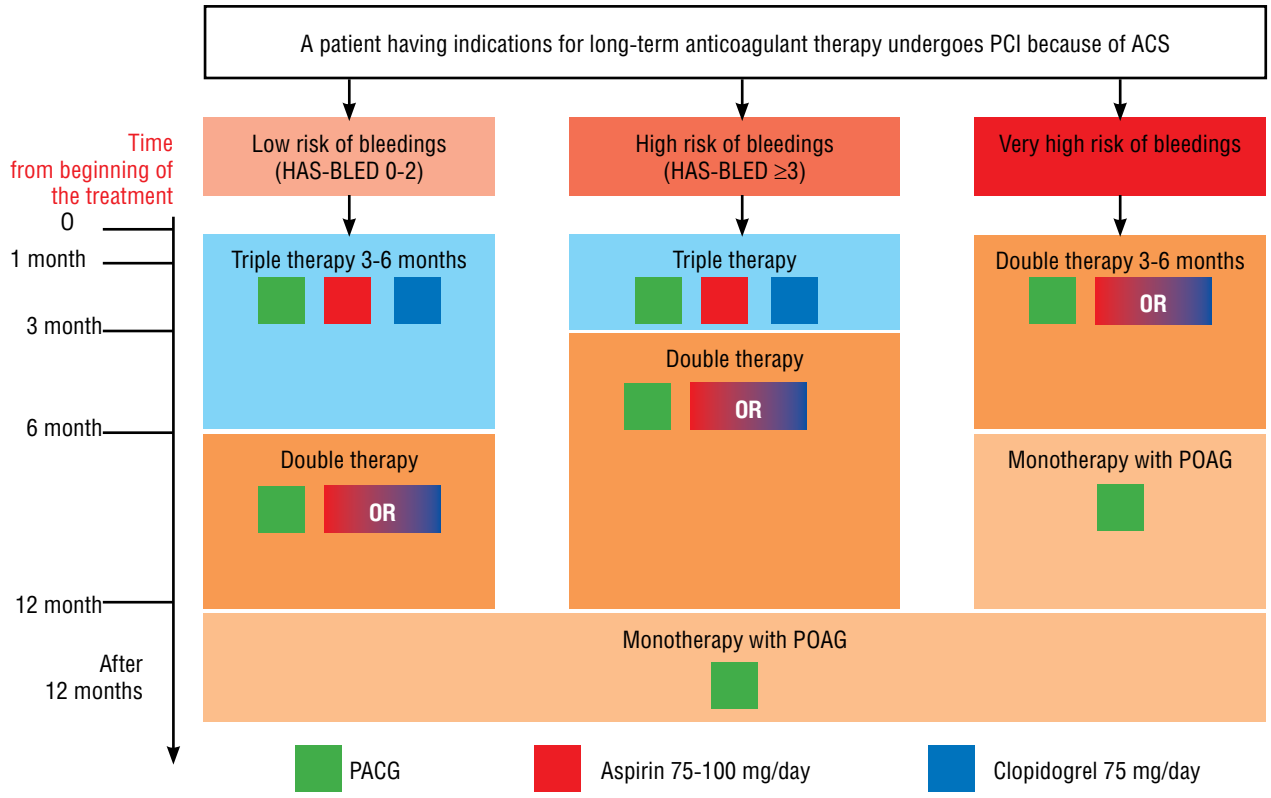

Figure 14. Algorithm for administration of the antithrombotic therapy after PCI in patients with ACS receiving peroral anticoagulants [2,155]

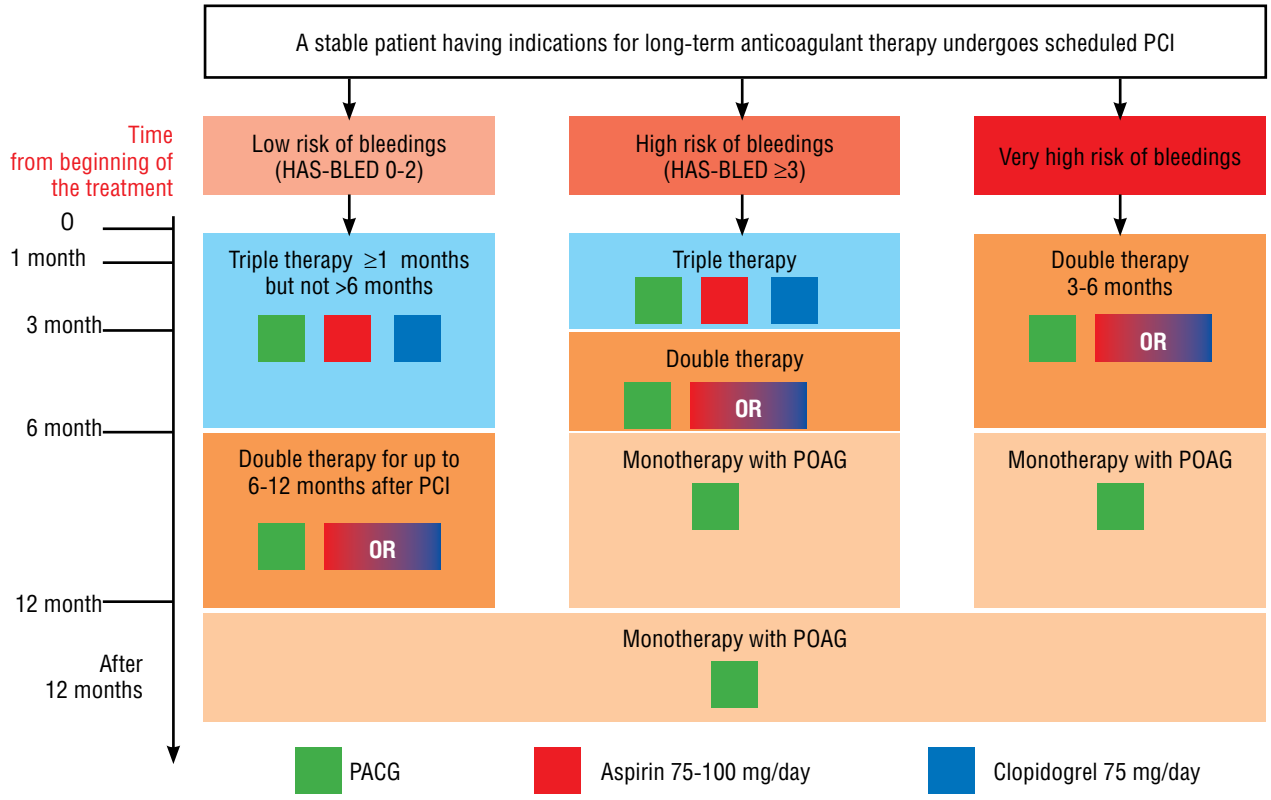

Figure 15. Algorithm for administration of the antithrombotic therapy after scheduled PCI in patients with stable CHD receiving peroral anticoagulants [2, 155]

(with reaching INR values to the lower limit of the therapeutic range) without switching to heparin. Then the treatment with Warfarin should be resumed in the maintenance dose, which is "usual" for this patient, without the use of the loading dose, in the evening on the day of the surgery or in the next morning provided that hemostasis is adequate.

Table 23. Recommendations on the period of DPACG withdrawal in case of scheduled invasive/ surgical interventions

	Dabigatran		Rivaroxaban		Apixaban	
Risk of bleedings	Low/stadard risk	High risk of bleeding/ extensive surgery	Low/stadard risk	High risk of bleeding/ extensive surgery	Low/stadard risk	High risk of bleeding/ extensive surgery
CC ≥80 ml/min	≥24 hours	≥48 hours	≥24 hours	≥48 hours	≥24 hours	≥48 hours
CC 50-80 ml/min	≥36 hours	≥72 hours	≥24 hours	≥48 hours	≥24 hours	≥48 hours
CC 30-50 ml/min	≥48 hours	≥96 hours	≥24 hours	≥48 hours	≥24 hours	≥48 hours
CC 15-30 ml/min	Not indicated	Not indicated	≥36 hours	≥48 hours	≥36 hours	≥48 hours
CC <15 ml/min			Not indicated		Not indicated	

Note: CC – creatinine clearance

If it necessary to perform a surgical or diagnostic procedure associated with the risk of bleeding in a patient with AF and rheumatic valvular heart disease/ mechanical cardiac valve prosthesis or high risk of thromboembolic complications (IS or TSA in the nearest 3 months or total CHADS2 score = 5-6), one should consider the possibility to stop temporarily the use of vitamin K antagonists with switching to non-fractionated or low molecular weight heparin in the doses used in the treatment of venous thrombosis (use the "bridging therapy"). The parenteral administration of anticoagulants may be resumed after the surgery when stable hemostasis is ensured (optimally in the first 12-24 hours after the surgery, but this term may be extended to 48-72 hours after major interventions and in case of high risk of bleedings). If there is no bleeding, the administration of vitamin K antagonist should be resumed also in the dose selected earlier. The parenteral administration of anticoagulants may be stopped not earlier that 5 days after resumption of intake of vitamin K antagonists and not earlier than two successive days with INR being at least at the lower limit of the therapeutic range [1-2].

Taking into account the rapid beginning of action and prognosticated period of its stopping, DPACG do not require the transition therapy with low molecular weight heparins [156]. But considering the risk of perioperative bleedings, DPACG should also be withdrawn in case of surgical interventions and the withdrawal duration depends on the risk of bleeding during the surgical intervention and functional state of the kidneys (see algorithm in Table 23).

If there are doubts concerning stopping of the anticoagulation effect of DPAC some laboratory tests can be used (APTT or thrombin time in dilution for Dabigatran, or prothrombin time anti-Xa activity test with chromogenic substrates for Rivaroxaban and Apixaban). But such strategy was never studies in clinical trials and cannot be recommended for routine use [156].

After the surgery, the administration of new peroral anticoagulants may be resumed immediately after achieving the effective hemostasis.

9.8. Bleeding which developed during the therapy with peroral anticoagulants

9.8.1. The treatment of bleedings which developed during the therapy with peroral anticoagulants

In spite of long-term clinical experience, bleedings in patients receiving peroral anticoagulants still remain the basic danger of the therapy. For patients receiving the long-term anticoagulant therapy, registration of minor and clinical significant moderate hemorrhages in addition to fatal and life-threatening ones is important for assessment of the treatment safety. Division of bleedings into massive, moderate clinically significant and minor ones was suggested in the large-scale GARFIELD-AF register of patients with atrial fibrillation [160].

It should be emphasized that according to recent data, the rate of massive bleedings during ACTh does not exceed 2-5% annually [161], and it should be mentioned that the rate of bleedings basing the findings of clinical trials is as a rule lower than that when the same antithrombotic drugs are used in actual clinical practice. But the high risk of bleedings a priori should not be the only one ground for refusal from anticoagulants in patients with AF of high risk.

If bleedings develop during the therapy with peroral anticoagulants, it is necessary to reveal a bleeding source, assess more precisely its recentness and estimate bleeding severity. It is also necessary to determine more precisely the time of the last intake of anticoagulant and assess presence of other factors increasing the risk of bleeding

Table 24. Determination of bleeding type according to GARFIELD-AF register [160]

Massive hemorrhagic complications	Evident bleeding associated wit at least one sign of the following: • decreased of hemoglobin level by ≥2 g/dl or • need in hemotransfusion of ≥2 blood doses • having clinically significant localization (intracranial, intraspinal, intraocular, heart tamponade, intraarticular, intramuscular with compression syndrome, retroperitoneal) • fatal
Moderate clinically significant hemorrhagic complications	Evident bleeding which did not reach criteria of "massive" bleeding but which required medical intervention, change of the therapeutic regimen by a doctor or was associated with pain, discomfort or change in the patient's habitual activity
Minor hemorrhagic complications	All other bleedings not meeting the criteria of "massive" and "moderate clinically significant" bleedings

(concomitant therapy, chronic kidney disease, alcohol abuse) and concomitant therapy. Hemoglobin level hematocrit, thrombocyte number, creatinine clearance should be assessed of out laboratory tests. INR and APTT should be determined in patients receiving VKA. The coagulation tests performed during the treatment with DPACG do not provide the full information, nevertheless, increased APTT in case of use of Dabigatran evidences its presence in the blood. So, diluted thrombin time (Hemoclot test) can be helpful also during the treatment with Dabigatran and determination of anti-Xa factor activity can be useful during the treatment with Xa factor inhibitors [156].

The treatment of any bleeding is based on the search and removal of its source. In case of acute bleeding one can speak of surgical or endoscopic hemostasis, mechanical vessel compression. In case of massive bleeding it is often required to restore hemodynamic parameters by fluid volume replacement, and rarer by the use of inotropic support. Blood transfusion should not be administered without critical necessity. The blood component transfusion is not a method for correction of hemodynamic parameters. The decrease of hemoglobin level to less than 7 g/dl and lowering of hematocrit to less than 25% is the grounds for transfusion of packed red cells. The platelet concentrate may be transfused in case of continuing life-threatening bleeding, in spite of all above measures and decrease of thrombocyte number to less than 60 thousand/μl. The long-term therapy with iron preparations is indicated further in case of massive bleeding. The administration of erythropoietin is not justified taking into account the increased risk of thromboembolic complications.

The optimum method to neutralize the action of VKA consists in parenteral administration or peroral intake of vitamin K1, which is not available in RF. Vicasol, which is available on the home pharmaceutical market, is the K2 vitamin precursor; its action develops very slowly, therefore, administration of Vicasol for the treatment of acute bleeding with simultaneous treatment with VKA is not effective. The peroral intake of Phytomenadione, which is available in Russia, makes a patient resistant to the action of indirect anticoagulants for 7-10 days and, therefore, it should not be used in these clinical situations.

The preferable approach consists in administration of prothrombin complex concentrate (PCC) containing coagulation factors, the synthesis of which is blocked by VKA, and also proteins C and S. The coagulation factor concentration in PCC is 25 times higher than that in the plasma. The PCC dose is 25 IU/kg for baseline INR = 1.9-3.5, 35 IU/kg for INR=4.6-6.0 and 50 IU/kg for INR of more than 6.0 for full neutralization of VKA action (INR ≤ 1.2).

It was shown that intake of 50 g of activated carbon lowered absorption of Dabigatran (if it was taken not ore than 2 hours ago) and, possibly, Rivaroxaban and Apixaban (if they were taken not more than 4-6 hours ago). Dabigatran elimination can be significantly increased by hemodialysis. If anticoagulant was taken not long ago or overdosage of DPACG is suspected, gastric lavage may be performed.

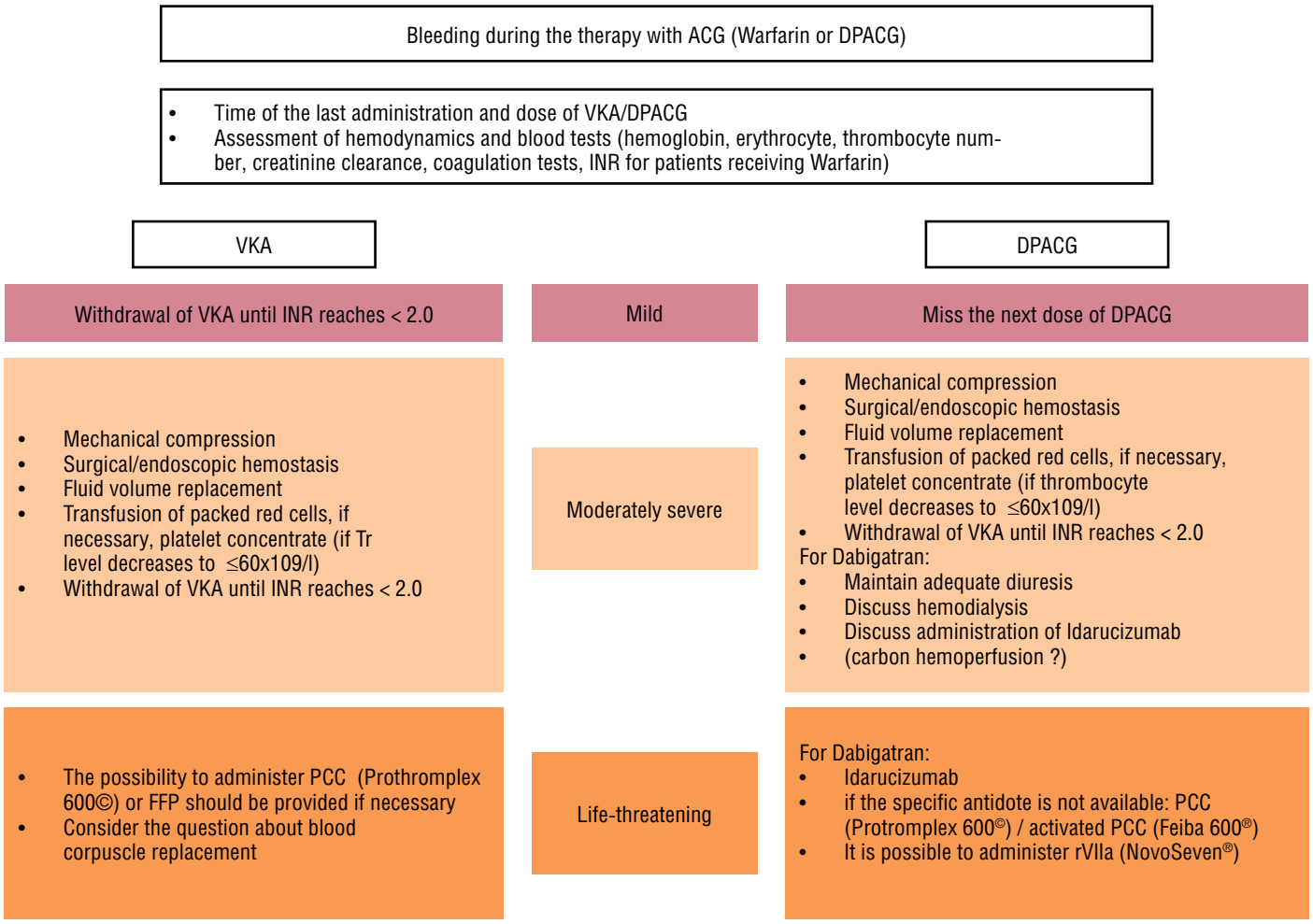

Figure 16. The strategy for treatment of patient suffering from AF with active bleeding, which developed during the therapy with peroral anticoagulants

ACG – anticoagulants, DPACG – direct peroral anticoagulants, INR – international normalized ratio, VKA – vitamin K antagonists, Tr – thrombocytes, PCC – prothrombin complex concentrate, FFP – fresh frozen plasma

Severe bleedings including those requiring an emergency surgical intervention, make it necessary to stop the action of anticoagulants. At present two drugs are approved for use: Idarucizumab, the specific antidote against Dabigatran, and Andexanet alfa, which is a specific antagonist of Xa factor inhibitors. Idarucizumab has been registered in RF since the end of 2018. The recommended dosing regimen of Idarcizumab is two boluses or two successive infusions of 2.5 g of the drug. Another specific antagonist of Xa factor inhibitors, Ciraparantag, is also at the stage of clinical trials. If specific antidotes are not available, it is possible to use the prothrombin complex concentrate, preferably, its activated form, in the dose of 50 U/kg body weight (the daily dose should not exceed 200 U/kg body weight). The activated recombinant factor VII in the dose of 90 μg/kg can be used as a drug of the second line [162-164]. The administration of a specific antidote or PCC without any preliminary analyses is justified only in patients with life-threatening bleedings (e.g., intracranial bleedings) or in those patients, for whom an emergency surgical intervention is indicated because of life-threatening condition (e.g., for aortic aneurysm rupture). In all other situations one should assess whether the anticoagulant is present in the blood in a sufficient quantity, i.e, whether the substrate is available for administration of the drug stopping the action of DPACG. If such drug has been administered, the coagulation tests performed over time, allow to assess the efficiency of stopping of the anticoagulant action [165].

Minor bleedings require only temporary withdrawal of anticoagulants (VKA should be withdrawn until INR lowers to < 2.0 and DPACG should be withdrawn for 1 day). it is important to explain to a patient the significance of compliance for the therapy and baselessness of refusal from intake of ACTh even in case of recurrence of minor bleedings.

9.8.2. Resumption of the antithrombotic therapy after bleeding

In accordance with the consensus of the task force on thromboses of the European Society of Cardiology dated 2017, the tactics of the antithrombotic therapy after developed bleeding is determined by the ratio of the risk of ischemic and hemorrhagic complications [165].

The category of the high risk of bleeding recurrence includes intracranial or life-threatening extracranial bleedings, which developed without visible provoking factors (e.g., injury, invasive intervention, arterial hypertension, antithrombotic drug overdosage), when any therapeutic methods are impossible or ineffective or a bleeding source has been found but it is unremovable. Patients with very high risk of thrombosis and simultaneous very high risk of repeated bleedings are the most difficult and require the individual collegial decision made by a multidisciplinary team. Nevertheless, if the risk of thrombosis is higher than the risk of repeated bleeding, the antithrombotic drug should not be withdrawn. The category of patients with high/very high risk of ischemic stroke includes patients with AF with CHA_2DS_2-VASc score ≥4, patients with mechanical cardiac valve prostheses or circulatory support devices.

The anti-thrombotic drug can be withdrawn only for a short period until the patient's condition stabilizes in case of the comparable risk of thrombosis and bleeding. If the risk of bleeding is higher than the probability of ischemic complications, the drug should be withdrawn until the patient's condition stabilizes, and then it is necessary to consider the decrease of the number and/or dose of antithrombotic drugs taken for a long period. Specific cases, which are the most common in the clinical practice in accordance with recommendations given by the experts of the task force on thromboses of the European Society of Cardiology are considered below [165].

Anticoagulant therapy after intracranial bleeding

- ACTh may be resumed in most cases 1 week after previous extracranial bleeding (the risk of thromboembolic complications the most often exceeds already the probability of repeated bleeding by this time).
- If an antidote (e.g., Idarucizumab) was used to stop the action of DPACG, ACTh should be resumed as early as possible (preferably, in 3-4 days if the individual risk profile allows this).
- When resuming DPACG, the renal function should be assessed to avoid the excessive drug accumulation and increased risk of bleeding.
- The administration of Dabigatran and Rivaroxaban is associated with the increased risk of GIB. If a patient has GIB during the therapy with these drugs, switching to VKA or Apixaban should be considered.
- The withdrawal of VKA is associated with very high risk of valve thrombosis and SE in patients with mechanical heart valve prosthesis (especially in the mitral position), therefore, ACT should not be withdrawn in most cases in such patients.

Triple antithrombotic therapy after extracranial bleeding

- If bleeding develops in a patient with nonvalvular AF, who receives ACTh and two antiaggregants after PCI, one of antiaggregants should be withdrawn (Clopidogrel should not be withdrawn during the first month after PCI). For patients receiving Warfarin, INR should be maintained i the range of 2.0-2.5; the time in the therapeutic rage of INR should be not less than 65-70%. DPACG should be administered in the minimum doses, which are effective for prevention of stroke (Dabigatran should be prescribed in the dose of 110 mg twice daily and other drugs should be administered in the full dose if there no additional criteria for its reduction according to the instruction for use).
- The double antiaggregant therapy may be administered after bleeding in patients with nonvalvular AF and the low risk of stroke (CHA_2DS_2-VASc score = 1 in males or 2 in females) receiving the combined therapy including anticoagulants for 12 months after PCI/ACS.

9.9. Anticoagulant support of cardioversion

The sinus rhythm recovery in patients with atrial fibrillation may be complicated with stroke or systemic thromboembolism [166]. The rate of such complications is on average 5-7% while the use of preventive anticoagulant therapy can lower this risk to the level of less than 1%. The maximum risk of thromboembolic complications is observed during the first 72 hours after cardioversion (CV); the predominant percentage of unfavorable events takes place during the first 10 days [166-167].

Thromboembolism occurs the most often at the moment of the sinus rhythm recovery due to separation of thrombotic masses formed earlier in the left atrium an its auricle. A thrombus is separated from the atrium wall because of increased myocardial contractility during the sinus rhythm as compared to atrial fibrillation. Thrombosis can develop somewhat rarer in the left atrium after the sinus rhythm recovery due to atrial myocardium stunning which contracts poorly yet for some time and releases paracrine factors increasing thrombogenicity of the left atrium endocardium. The degree of such transient myocardium dysfunction depends on the duration of AF episode.

Just therefore AF episodes should be divided by their duration from practical view point: less than 48 hours and more than 48 hours (or of unknown duration). An AF paroxysm lasting for less than 48 hours is associated with relatively low risk of thromboembolism, therefore, CV may be carried out in such case without preliminary long-term therapy with anticoagulants.

The new data shows that CV is complicated with thromboembolic events significantly rarer if is was performed within the time period of less than 12 hours after onset of the rhythm disorder episode. So, in the study performed by I. Nuotio et al. [168] the rate of thromboembolic complications after cardioversion carried out within the first 12 hours with anticoagulants was 0.3% and it was 1.1% (p=0.004) in the intervals of 12-24 hours and 24-48 hours. Even patients with the low risk of stroke (CHA_2DS_2-VASc score 0-1) had thromboembolic complications with the rate of 0.2% in case of cardioversion within the first 12 hours, 0.4% in the interval of 12-24 hours ad 0.9% in the interval of 24-48 hours (p=0.06 for differences between groups). In the FinCV retrospective analysis [166] the rate of stroke developed during cardioversion in patients with CHA_2DS_2-VASc score ≤1 and duration of AF episode of less than 48 hours, who did not receive anticoagulants, was 0.4% (10 cases per 2772 patients) while patients receiving anticoagulants had no strokes. Basing on the presented data, any CV should be performed with simultaneous anticoagulant support.

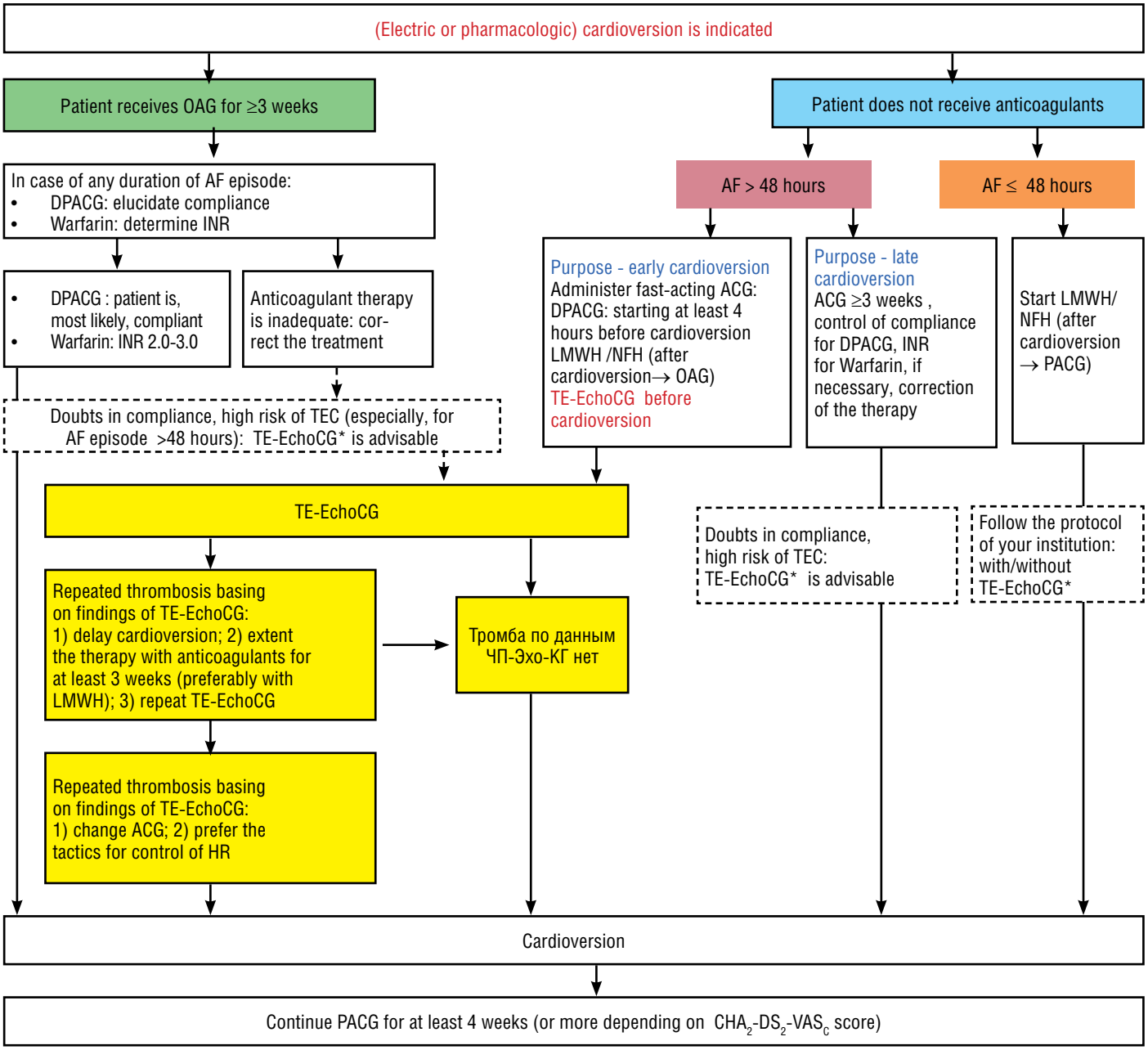

Figure 17. Algorithm for anticoagulant support of cardioversion in patients with AF (according to [170] with modifications)

**according to the current recommendations of the European Society of Cardiology (2016) [2], TE-EchoCG is not obligatory in these clinical situations. It is the most advisable to perform this study in patients with the high risk of thromboembolic complications (and LA thrombosis, respectively) and also if there are doubts in the compliance for the treatment with anticoagulants. A protocol should be developed to each specific clinic taking into account its technical resources and experience of the staff; this protocol would regulate the use of TE-EchoCG before cardioversion. PACG – peroral anticoagulants, AF – atrial fibrillation, LMWH – low molecular weight heparins, NFH – non-fractionated heparin, TEC – thromboembolic complications, DPACG – direct peroral anticoagulants.*

An atrial fibrillation episode lasting for ore than 48 hours or of unknown recentness

If an atrial fibrillation episode lasts for more than 48 hours or recentness of its onset is unknown, in this case there are two approaches to prevention of thromboembolic complications associated with cardioversion (Fig. 17). The first approach consists in administration of the anticoagulant therapy at east for 3 weeks before CV and for 4 weeks after it. The anticoagulants are administered for this period irrespective of the risk of stroke and systemic thromboembolism as per CHA_2DS_2-VASc scale and the method for sinus rhythm recovery (electric or pharmacological method). The peroral anticoagulants (DPACG or Warfarin are used). It is critically important to make sure that the optimum anticoagulation level is ensured for the whole period of the treatment. INR in patients receiving Warfarin should be in the target range of 2.0-3.0. Patients receiving DPACG should be interviewed in detail about their compliance for the treatment, their answers should be recorded in the medical documentation. If a patient missed at least one daily dose of DPACG (1 intake for Rivaroxaban, 2 intakes for Apixaban and Dabigatran) during 3 weeks preceding cardioversion, he (she) is considered as not having compliance for the treatment, and 3 weeks should be counted again from that moment when he(she) started to take the drug without missing the daily dose. If there are doubts regarding the compliance for the treatment, TE-EchoCG should be performed before cardioversion even if the previous therapy with DPACG formally was long (≥3 weeks) [2, 169].

If a patient receives already any peroral anticoagulant, it is necessary to continue its administration and assess adequacy of anticoagulation in the previous 3 weeks. If a patient received anticoagulants during this period and the degree of anticoagulation is optimum, cardioversion may be performed immediately. If a patient did not receive anticoagulants earlier or he(she) interrupted their intake, anticoagulant should be administered de novo. Warfarin is prescribed simultaneously with parenteral administration of low molecular weight or non-fractionated heparin in the doses recommended for the treatment of venous thrombosis (e.g., Enoxaparin in the dose of 1 mg/kg body weight twice daily, NFH in the dose of 450 U/kg body weight daily in 2-3 injections subcutaneously). The combined administration of heparin and Warfarin continues for not less than 5 days until INR in two successive measurements does not reach values ≥2. After that heparin is withdrawn and the treatment with Warfarin is continued. As DPACG start to act to the full extent several hours after intake of the drug they are administered without heparin [2]

According to the currently available data (subanalyses of RE-LY, ROCKET-AF, ARISTOTLE, ENGAGEAF-TIMI 48 studies and also X-VeRT, ENSUREAF, EMANATE studies) Warfarin and DPACG are comparable in efficiency regarding prevention of systemic embolism during cardioversion [171].

In this situation DPACG are superior regarding greater predictability of the action, absence of time loss for selection of the drug dose. The time before cardioversion in anticoagulant-naive patients, to whom DPACG were administered, even at specialized anticoagulation clinics is lower by 20-30% than that in patients receiving Warfarin. Considering the data of different clinics, the average time required for selection of the adequate dose of Warfarin before cardioversion may be drawn out for up to 12 weeks. Thus, the selection of DPACG can shorten the expectation time of the procedure, makes it possible to schedule the accurate date for it, what, in its turn, will lower the psycho-emotional stress for a patient.

TE-EchoCG for ruling out the presence of thrombi in the left atrium can serve as an alternative to relatively long preliminary treatment with anticoagulants [172]. Besides that, CV under control of TE-EchoCG can be used in those cases when the patient's condition requires fast sinus rhythm recovery or shortened duration of the anticoagulant therapy (because of patient's refusal or risk of bleedings), if there are doubts in patient's compliance for the treatment with anticoagulants or in case of high clinical probability of thrombus presence in LA and its auricle [2].

If there are no thrombi in the LA cavity and auricle CV may be performed. The thrombus absence before cardioversion does not eliminate the need to administer the anticoagulant therapy before, during and after rhythm recovery because a thrombus can be formed newly under conditions of LA myocardium "stunning". In order to provide for the adequate anticoagulation during cardioversion, it is possible to administer Warfarin (minimum 5 days before scheduled cardioversion; the procedure should be performed with INR in the range of 2.0-3.0), DPACG (at least one dose not less than 4 hours before cardioversion) and also NFH in the form of intravenous infusion or LMWH in the form of subcutaneous injections in doses used for the treatment of venous thrombosis [173].

It is important to emphasize that adequate anticoagulation is provided for at first, then TE-EchoCG is performed; if there is no thrombus, CV is carried out as soon as possible.

If TE-EchoCG reveals a thrombus (or spontaneous echo-contrasting phenomenon of degree III-IV), CV is not performed. The anticoagulant therapy is continued for not less than 3 weeks more. If a thrombus has been formed in LA with previous anticoagulant therapy, its adequacy should be assessed (the time in the therapeutic range of INR for Warfarin, compliance for the treatment for DPACG). According to the findings of some studies and also basing on the experience of our clinic, the optimum results regarding thrombus dissolution can be achieved by using LMWH (Enoxaparin in the dose of 1 mg/kg body weight 2 times daily subcutaneously). TE-EchoCG should be repeated after a repeated period of the treatment (not less than 10-14 days when using Enoxaparin) [174].

If a thrombus is dissolved, CV may be performed. If a thrombus is preserved, cardioversion is not allowed. The tactics for heart rate control may be selected in this case, especially, if the target HR values are not achieved. The change of anticoagulant should be considered [96].

The question on the necessity to perform TE-EchoCG before cardioversion after adequate three-week anticoagulation still remains open. This manipulation in principle is not essential. But there is data that such investigation reveals a thrombus in the LA auricle in 6% of cases [175]. It is important that the above investigation revealed a thrombus in LA auricle after 3 weeks of adequate anticoagulant therapy only in patients with lowered LV function (LV EF <40%); all these patients had CHA_2DS_2-VASc score ≥5. The rate of LA auricle thrombosis in this patient category was 17.9% in spite of the treatment. According to our opinion, if it is possible to perform TE-EchoCG before cardioversion, especially scheduled one, this should be done, first of all, in patients with the high risk of thromboembolic complications.

When AF episode lasting for more than 48 hours is revealed, it is necessary to provide as soon as possible the adequate anticoagulation with DPACG or LMWH/NFH with further transition to vitamin K antagonists irrespective of the strategy chosen by an attending physician (early CV after TE-EchoCG or late CV after administration of anticoagulants for 3 weeks).

The beginning of the anticoagulant therapy should not delay the emergency cardioversion in patients with AF paroxysm and instable hemodynamics or acute myocardial ischemia caused by the paroxysm irrespective of its duration. According to our opinion, it is advisable in this case to administer parenteral anticoagulants (NFH or LMWH) intravenously and then to switch to peroral anticoagulants. Nevertheless, it should be noted that any special clinical trials for search of the optimum strategy of anticoagulation in this situation were not performed.

The anticoagulant therapy is to be continued for 4 weeks after cardioversion. The necessity of further long-term anticoagulant therapy is assessed after the period basing on stratification of the risk of thromboembolic complications as per CHA_2DS_2-VASc scale. If the risk of thromboembolism is high (CHA_2DS_2-VASc score $\geq$1 in males and $\geq$2 in females), the anticoagulant therapy is continued indefinitely (for the term of life) even in case of preserved sinus rhythm after cardioversion and anticoagulants may be withdrawn in case of low risk [2].

AF episode lasting for less than 48 hours

If the duration of AF episode is less than 48 hours, CV may be performed without preliminary long anticoagulant preparation and TE-EchoCG [176].

Nevertheless, anticoagulants should be administered to all patients (with both high and low risk of stroke) before cardioversion. If a patient did not receive peroral anticoagulants, the parenteral administration of heparin (non-fractionated or low molecular weight heparin) is used as a rule in his situation with subsequent scheduled transition to peroral anticoagulants [2]. Today the data on how safe the administration of one dose of DPACG and cardioversion without TE-EchoCG would be is restricted by a small sample of such patients from the EMANATE study (n=753) [177]. The European experts do not recommend such approach yet [2], while recommendations of AHA/ACC of 2019 on management of patients with AF allow the use of DPACG in such clinical situation [96].

If a patient already receives peroral ACG, it is necessary to assess anticoagulation adequacy (estimate patient's compliance for the treatment with DPACG, and determine INR for Warfarin); if necessary, the treatment should be corrected and cardioversion should be carried out.

As we already said above, some risk of thromboembolic complications is present also in case of relatively short duration of AF episode. Therefore, evidently, it is justified to perform TE-EchoCG before cardioversion even if the AF paroxysm duration is less than 48 hours in patients with very high risk of thromboembolic complications, lowered LV EF, in case doubts in compliance.

It is advisable to develop the standard protocol for performing cardioversion at each specific clinic taking into account its equipment, technical resources and experience of the staff and follow this protocol in future.

The data on the risk of thromboembolic complications in patients with atrial flutter is limited. But there is evidence of thrombus formation in LA in patients with this rhythm disorder and also transition of atrial flutter to AF, therefore, according to most experts, the tactics of the anticoagulant therapy in case of atrial flutter is similar to that in patients with AF [2].

The anticoagulant prevention algorithm does not depend on the method for sinus rhythm recovery (pharmacologic or electric method).

It is preferable to perform TE-EchoCG before CV to patients with implantable devices for occlusion of the LA auricle and isolation of the LA auricle using surgical methods. This is associated with the fact that the junction between the LA cavity and its auricle may be preserved in patients who underwent these procedures. The presence of the residual blood flow can increase significantly the risk of thromboembolic complications (even to a greater extent than before the procedure of ALA isolation), especially, if patients do not receive the anticoagulant therapy. Besides that, TE-EchoCG not infrequently reveals an asymptomatic thrombus on the occluder surface which also can be the cause of systemic embolism in case of cardioversion [178].

9.10 Anticoagulant therapy before, during and after the procedure of radio frequency and cryoablation for atrial fibrillation

If a patient scheduled for ablation does not receive peroral anticoagulants, they should be administered minimum 3 weeks before scheduled intervention (especially to patients with high risk of TEO, persistent AF form) [88]. TE-EchoCG should be performed before ablation: LA auricle or cavity thrombosis, high degree of spontaneous Echo-contrasting are a contraindication for ablation.

Ablation for AF is associated, on the one side, with the high risk of thromboembolic complications and, on the other hand, with the high risk of bleedings (especially, if the interatrial septum is punctured without additional visualization) [88]. Such risk profile preconditions the intervention without withdrawal of peroral anticoagulants. If ablation is performed during the therapy with Warfarin, INR on the day of the intervention should be 2.0-2.5. The results of VENTURE-AF [179], RE-CIRCUIT [180], AXAFA-AFNET 5 [181] and ELIMINATE-AF [182] studies suggest that ablation may be also performed with simultaneous treatment with DPACG. The last intake of the drug should take place not less than 12 hours before the intervention.

NFH should be administered just during ablation with reaching the activated coagulation time (ACT) of 300-350 s [183]. One should remember that heparin dose and time from the moment of its injection can be more during the therapy with DPACG for achieving the target ACT values (this is associated with the direct interaction between DPACG and ACT test). It is advisable to administer Protamine Sulfate after completion of the procedure. The therapy with DPACG may be resumed 3-5 hours after removal of the introducer provided that hemostasis is adequate and there are no signs of hemopericardium [155]. It should be noted that ablation without withdrawal of peroral anticoagulants is the optimum tactics minimizing the risk of thromboembolism and bleedings (as compared also to tactics of the "bridging therapy") [184].

Peroral anticoagulants should be administered minimum for 2 months after ablation. Further the need in administration of anticoagulants is determined by the standard algorithm for patients with AF basing in CHA_2DS_2-VASs score irrespective of ablation success, i.e. performing ablation in patients with the high risk of thromboembolic complications does not free from the necessity to take anticoagulants [180]. This is caused by the fact that ablation efficiency on average does not exceed 70%; AF often becomes

asymptomatic what does not exclude the probability of stroke or systemic thromboembolism. If a patient insists on withdrawal of anticoagulants because symptomatic AF is absent, multi-day ECG monitoring should be performed to rule out AF recurrence.

The basic provisions on prevention of stroke and systemic thromboembolism in patients with atrial fibrillation are presented in Table 25.

REFERENCES

References published on pages 43-49

Table 25. Basic recommendations for prevention of stroke and systemic thromboembolism in patients with atrial fibrillation

Recommendation	Class	Level	Reference
General provisions			
It is recommended to use the CHA_2DS_2-VASc in order to assess the risk of stroke in patients with nonvalvular atrial fibrillation.	I	A	1,2
The selection of the antithrombotic therapy should be based on the ratio between absolute risks of stroke/ thromboembolism and bleedings and also on the assessment of the total clinical benefit for a specific patient.	I	A	1,2
The assessment of the risk of bleeding in all patients is advisable before administration of the antithrombotic therapy in order to reveal the modifiable risk factors of hemorrhagic complications	IIA		1,2,138
The permanent administration of peroral anticoagulants with the purpose of prevention of thromboembolic complications is recommended to male patients having the total CHA_2DS_2- VASc score ≥ 2	I	A	1,2
The permanent administration of peroral anticoagulants with the purpose of prevention of thromboembolic complications is recommended to female patients having the total CHA_2DS_2- VASc score ≥ 3	I	A	1,2
Administration of peroral ACG with the purpose of prevention of thromboembolic complications can be recommended to males with CHA_2DS_2-VASc score = 1 taking into account the patient's individual features and preferences	IIa	B	1,2
Administration of peroral ACG with the purpose of prevention of thromboembolic complications can be recommended to females with CHA_2DS_2-VASc score =2 taking into account the patient's individual features and preferences	IIa	B	1,2
If VKA are administered, it is recommended to achieve the maximum time in the therapeutic range of INR (2.0-3.0) which should be estimated regularly.	I	A	1,2
Only VKA (INR≥2.0-3.0) are recommended for patients with moderate or severe mitral stenosis or with mechanical artificial valve.	I	B	1,2
If the anticoagulant therapy is administered for the first time direct peroral anticoagulants (Apixaban, Dabigatran, Rivaroxaban) are superior to Warfarin (provided that there are no contraindications for their administration)	I	A	1,2,134-136
If INR is often outside the therapeutic range (<65%) during the therapy with Warfarin, administration of DP ACG should be considered (if there are no contraindications). Switching from VKA to DP ACG is also possible in accordance with patient's wishes.	IIb	A	1,2,134-136
The routine combination of ACG with antithrombocytic drugs increases the risk of bleedings therefore, it is not recommended for patients if additional indications are absent.	III	B	1,2
It is not recommended to administer the anticoagulant or antiaggregant therapy in males and females with AF when there are no risk factors of thromboembolic complications	III	B	1,2
The monotherapy with antithrombocytic drugs is not recommended for prevention of stroke in patients with AF	III	A	1,2
DPACG are not recommended to patients with mechanical heart valves	III	B	1,2
DPACG are not recommended to patients with moderate and severe mitral stenosis	III	C	1,2
Prevention of thromboembolic complications in patients undergoing cardioversion			
If cardioversion is scheduled, the therapy with LMWH, NFH (in the doses approved for the treatment of venous thrombosis) or DPACG should be started as soon as possible to all patients who do not receive anticoagulants for a long period.	IIa	B	1,2

If the duration of AF episode is 48 hours and more or if the duration of the rhythm disorder episode is unknown, the-duration of the anticoagulant therapy before cardioversion should be not less than 3 weeks. For this purpose peroral anticoagulants should be used: Warfarin (INR 2.0-3.0), Apixaban, Dabigatran or Rivaroxaban. The beginning of the therapy with Warfarin should be combined with the treatment with NFH or LMWH until the target range of INR is reached (not less than 5 days). The anticoagulant therapy is indicated irrespective of CHA_2DS_2-VASs score and the method for sinus rhythm recovery (pharmacologic or electric method)	I	B	1,2
If early cardioversion is scheduled for a patient with AF episode lasting for less than 48 hours who does not receive the anticoagulant therapy, administration of NFH or LMWH (in the doses approved for the treatment of venous thrombosis) should be started as soon as possible	I	C	1,2
If a patient not receiving the anticoagulant therapy has indications for emergency cardioversion because of hemodynamic instability or acute myocardial ischemia, administration of NFH or LMWH (in the doses approved for the treatment of venous thrombosis)	I	C	1,2
The duration of the anticoagulant therapy should be not less than 4 weeks after any cardioversion If NFH or LMWH was administered initially, it is advisable to switch a patient to peroral anticoagulants	I	B	1,2
In 4 weeks after cardioversion a decision should be made on the necessity of the anticoagulant therapy basing on the risk of stroke (CHA_2DS_2-VASs score). The therapy with peroral anticoagulants should be continued for the term of life in patients with risk factors of stroke even in case of stable preservation of the sinus rhythm after cardioversion.	I	B	1,2
The anticoagulation regimen in case of cardioversion in patients with atrial flutter is similar to that in patients with AF.	I	C	1,2
Ruling out the thrombus presence in the left atrium and its auricle with the help of transesophageal echocardiography with preliminary achieved therapeutic anticoagulation level is an alternative to long-term anticoagulation before cardioversion	I	B	1,2
If the transesophageal echocardiography reveals a thrombus in the left atrium, cardioversion is not allowed. The anticoagulant therapy should be continued at least for 3 weeks	I	C	1,2
If the repeated transesophageal echocardiography does not reveal a thrombus, cardioversion should be performed and the anticoagulant therapy should be continued for at least 4 weeks more	I	C	1,2,174
If the repeated transesophageal echocardiography revealed a preserved thrombus, cardioversion is not allowed. The issue should be considered on alternative tactics for the treatment (heart rate control)	I	C	1,2,174
The early cardioversion in a patient with AF episode lasting for less than 48 hours may be performed without TE-EchoCG.	IIa	B	1,2
Direct peroral anticoagulants (Apixaban, Dabigatran, Rivaroxaban) may not be used for the anticoagulant support of cardioversion in patients with mechanical heart valve prosthesis (level of evidence B) or moderate or severe mitral stenosis (level of evidence C)	III	B/C	1,2,169 171
Occlusion and isolation of the auricle of the left atrium			
A patient with AF and the high risk of stroke should continue the use of anticoagulants after surgical isolation or occlusion of the LA auricle	I	B	1,2
ALA occlusion may be considered as a method for prevention of stroke in patients with AF having contraindications for the long-term anticoagulant therapy (e.g., patients with history of life-threatening bleedings the cause of which cannot be removed)	IIb	B	1,2
Surgical occlusion or isolation of ALA can be considered as a method for prevention of stroke in patients with AF who are scheduled for cardiosurgical intervention	IIb	B	1,2,143
Surgical occlusion or isolation of ALA can be considered as a method for prevention of stroke in patients who are scheduled for a thoracoscopic surgery because of AF	IIb	B	1,2,143
Secondary prevention of stroke in patients with AF			
It is not recommended to administer NFH or LMWH to patients with AF immediately after ischemic stroke.	III	A	1,2
The compliance for the therapy should be assessed and optimized in patients with AF with previous ischemic stroke or transient ischemic attack during the anticoagulant therapy	IIa	C	1,2
The treatment with ACG should be interrupted for 3-12 days (depending on the results of risk assessment of bleeding and repeated stroke by a multidisciplinary specialist team) in patients receiving anticoagulants with history of moderate or severe stroke	IIa	C	1,2
For patients with AF with previous ischemic stroke the question should be considered on administration of Aspirin as a drug for secondary prevention before beginning or resumption of the therapy with peroral anticoagulants	IIa	B	1,2
Thrombolysis with the use of recombinant tissue plasminogen activator is not recommended in INR exceeds 1.7 (or APTT is beyond the reference values in patients receiving Dabigatran)	III	C	1,2

DPACG are the more preferable drugs than VKA or Aspirin in patients with AF with history of stroke	I	B	1,2
It is not recommended to administer the combined therapy with peroral anticoagulants and antiaggregants to patients with AF after ischemic stroke or TIA	III	B	1,2
Peroral anticoagulants may be resumed 4-8 weeks after intracranial hemorrhage in patients with AF provided that the cause of bleeding is removed and risk factors are corrected	IIb	B	1,2
Minimization of the risk of bleedings during the anticoagulant therapy. Management of patients with bleedings during the anticoagulant therapy			
The control of blood pressure level in patients with arterial hypertension allows to lower the risk of bleedings	IIa	B	1,2
If Dabigatran is administered to patients older than 75 years, the decreased drug dose (110 mg x 2 times daily) may be considered to lower the risk of bleedings	IIb	B	1,2
One should prefer VKA or other DP ACG as compared to Dabigatran in the dose of 150 mg twice daily, Rivaroxaban in the dose of 20 mg once daily or Edoxaban in the dose of 60 mg once daily in patients with the high risk of gastrointestinal bleeding	IIb	B	1,2,156
It is necessary to discuss refusal from alcohol use with patients receiving the therapy with peroral anticoagulants. The treatment should be suggested if necessary	IIa	C	1,2
The “bridging therapy” using NFH or LMWH should be administered to patients with AF and mechanical heart valve during the invasive intervention requiring withdrawal of Warfarin	I	C	96
The decision on the usefulness of the “bridging therapy” in patients with AF without mechanical heart valves should be based on the ratio between the risk of thromboembolism and bleeding and also the duration of Warfarin withdrawal period.	I	B	1,2,96
The routine assessment of genetic sensitivity to Warfarin is not recommended	III	B	1,2
Idarucizumab should be administered to a patient receiving Dabigatran in case of life-threatening bleeding or the need in emergency surgical intervention	I	B	96,156
The resumption of anticoagulants after a bleeding episode seems helpful in most patients. Such decision based on comparison of the risk and severity of repeated bleeding and thromboembolism should be made by a multidisciplinary team. The doctors’ conference should assess all possibilities for the anticoagulant treatment and other interventions for prevention of strokes, determine the tactics for maximum correction of risk factors of bleedings and stroke	IIa	B	1,2,96,156
It is recommended to interrupt the therapy with peroral ACG to patients with AF having symptoms of acute serious massive bleeding until the cause of bleeding is removed	I	C	1,2
Recommendations on the combined therapy with peroral anticoagulants and antiaggregants			
Administration of the triple antithrombotic therapy (peroral anticoagulants in combination with Aspirin and Clopidogrel) at least for 1 month irrespective of the stent type should be considered after a scheduled percutaneous coronary intervention in a patient with AF and the high risk of stroke	IIa	B	1,2,185
Administration of the triple antithrombotic therapy (peroral anticoagulants in combination with Aspirin and Clopidogrel) for the period of 1-6 months should be considered in patients with AF and the high risk of stroke undergoing PCI with stenting for ACS (and also in other clinical situations increasing the risk of thrombotic coronary complications)	IIa	C	1,2,185
The double therapy with peroral anticoagulants in combination with Clopidogrel in the dose of 75 mg daily as an alternative to the initial triple antithrombotic therapy if the risk of hemorrhagic complications exceeds the risk of ischemic complications	IIa	A	156,185
All patients undergoing PCI with stenting should receive Aspirin and Clopidogrel in the periprocedural period	I	C	185
DP ACG should be preferred over Warfarin in patients with AF and indications for the triple antithrombotic therapy	IIa	A	185
If a patient receives VKA in combination with Aspirin and Clopidogrel, one should maintain INR in the lower portion of the therapeutic range and try to achieve TTR > 65%	IIa	B	1,2,156 185
Switching to monotherapy with ACG should be considered 12 months after the event serving as the grounds for administration of the combined antithrombotic therapy	IIa	B	1,2,185
DPACG in combination with Aspirin and/or Clopidogrel should be administered in minimum doses approved for prevention of stroke	IIa	C	185
Rivaroxaban in combination with Aspirin or Clopidogrel may be administered in the dose of 15 mg/day	IIb	B	185
Dabigatran in combination with Aspirin or Clopidogral may be administered in the dose of 110 mg twice daily	IIb	B	185
It is not recommended to use Ticagrelor and Prasugrel as a component of the triple antithrombotic therapy in combination with Aspirin and ACG	III	C	156,185

List of abbreviations: List of abbreviations: VKA – vitamin K antagonists, ACG – anticoagulants, TTR – time in the therapeutic range, INR – international normalized ratio, LMWH – low molecular weight heparin, NFH – non-fractionated heparin, ACS – acute coronary syndrome, DPACG – direct peroral anticoagulants, ALA – auricle of the left atrium, AF – atrial fibrillation, PCI – percutaneous coronary intervention, TE-EchoCG – transesophageal echocardiography