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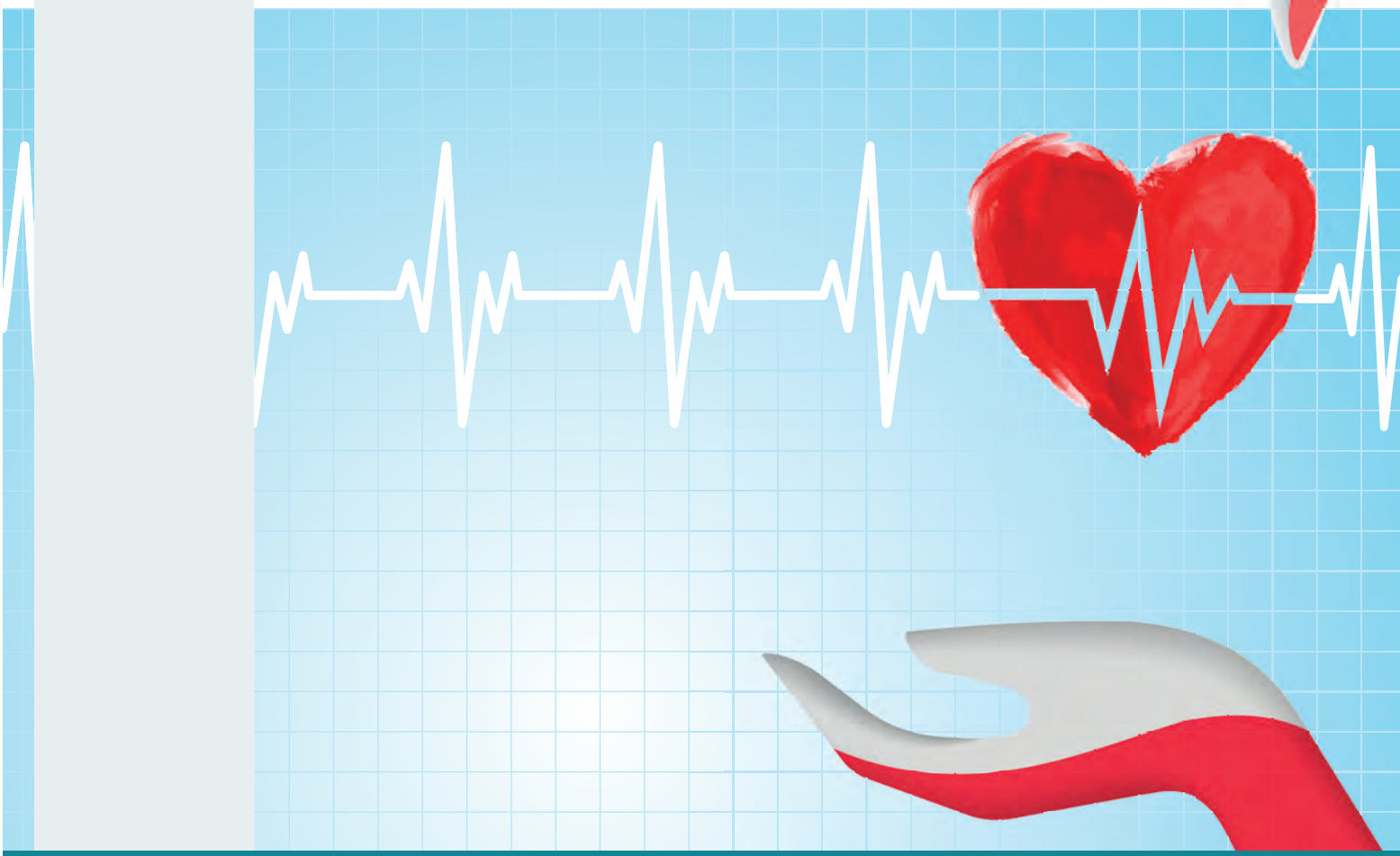

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Research Article

Recurrence of Arrhythmias after Thoracoscopic MAZE procedure

Vitaliy V. Lyashenko[1], Andrei V. Ivanchenko[1], Anzhelika S. Postol[1], Sardor N. Azizov[2], Alexander B. Vigovsky[1], Yuri A. Schneider[1]

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BACKGROUND: Thoracoscopic version of the MAZE operation alone or in combination with catheter ablation (hybrid approach) has become widespread in the treatment of atrial fibrillation (AFib). However, recurrences of arrhythmias after such operations, in particular recurrence of AFib, remain unresolved problem.

AIM: The aim of this study was to establish the structure of arrhythmia recurrence in patients with long-standing persistent AFib after primary epicardial ablation using the Dallas lesion set technique, as well as determining the optimal RFA strategy for recurrence.

METHODS: 138 catheter ablation procedures for 100 patients, who applied with recurrence of various atrial arrhythmias after thoracoscopic MAZE. 34 patients had 2 or more RFA (31 pts — 2, 2 pts — 3, 1 pts — 4).

RESULTS: After Dallas lesion set thoracoscopic ablation in the structure of recurrences dominated: 1 — AFib recurence; 2 — incisional left atrial flutter. After the operation, a potential arrhythmogenic substrate remains, which must be fully eliminated by RFA (in addition to ablation the main cause of recurrence). This minimally necessary intervention implies: control and reisolation of the pulmonary veins; control and reisolation of the posterior wall; septal line from the mitral valve to the right superior pulmonary vein with Y-shaped branch to the left superior pulmonary vein; cava-tricuspid isthmus-blockade. This will eliminate and prevent in the future potentially possible incisional arrhythmias in fragmentary scars after thoracoscopic MAZE procedure. The return of AFib represents the most difficult group of patients. Restoration of sinus rhythm in recurrent AFib after epicardial ablation is possible, but may require extensive ablations in both atriums, as a result of repeated procedures, until all potential arrhythmia mechanisms, present in a particular patient, are eliminated.

CONCLUSIONS: Catheter ablation remains the only method of effective treatment of recurrences after thoracoscopic MAZE procedure. The complexity and multicomponent nature of long-standing AFib causes the frequent need for repeated procedures, especially in cases of recurrence of atrial fibrillation.

Keywords: radiofrequency catheter ablation; atrial fibrillation; thoracoscopic MAZE; Dallas lesion set; hybrid approach; recurrence of atrial fibrillation; treatment of long-standing persistent atrial fibrillation.

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Научная статья

Рецидивы аритмий после торакоскопической процедуры MAZE

В.В. Ляшенко[1], А.В. Иванченко[1], А.С. Постол[1], С.Н. Азизов[2], А.Б. Выговский[1], Ю.А. Шнейдер[1]

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Актуальность. Торакоскопический вариант операции MAZE изолированно или в сочетании с катетерной абляцией (гибридный подход) получил широкое распространение в лечении фибрилляции предсердий. Однако рецидивы аритмий после таких операций, в особенности, рецидивы фибрилляции предсердий, остаются нерешенной проблемой.

Цель — изучение структуры рецидивов аритмий у пациентов с длительно-персистирующей фибрилляцией предсердий (ФП) после первичной эпикардиальной абляции по методике Dallas lesion set, а также определение оптимальной стратегии радиочастотной абляции (РЧА) при рецидивах.

Материалы и методы. Выполнены 138 процедур катетерной абляции 100 пациентам, обратившимся с рецидивами различных предсердных аритмий после торакоскопической модификации операции MAZE (34 пациентам — 2 и более; 31 человеку — 2, 2 пациентам — 3, 1 человеку — 4). У пациентов с 3 и более процедурами после торакоскопической операции рецидивирующей аритмией была фибрилляция предсердий.

Результаты. После торакоскопического варианта операции MAZE (по методике Dallas lesion set) в структуре рецидивов преобладают: 1 — возврат ФП, 2 — инцизионные левопредсердные трепетания, а также остается потенциально аритмогенный субстрат, который необходимо полностью устранять при катетерной РЧА (помимо работы с основной причиной рецидива). Такое минимально необходимое вмешательство подразумевает: контроль и реизоляцию легочных вен; контроль и реизоляцию задней стенки левого предсердия; септальную линию от митрального клапана до правой верхней легочной вены с Y-образным ответвлением к левой верхней легочной вене; кавотрикуспидальный истмус-блок. Это позволит устранить и предотвратить в будущем потенциально возможные инцизионные нарушения ритма по фрагментарным рубцам после торакоскопического MAZE. Пациенты с возвратом ФП представляют наиболее сложную группу. Восстановление синусового ритма при рецидивах ФП после торакоскопического варианта операции MAZE возможно с помощью повторных вмешательств, но может требовать обширных РЧА в обоих предсердиях в результате неоднократных процедур до устранения всех потенциальных механизмов ФП, присутствующих у конкретного пациента.

Выводы. Катетерная абляция остается единственным методом эффективного лечения рецидивов после торакоскопической процедуры MAZE, а сложность и многокомпанентность длительно-персистирующей ФП обусловливает частую необходимость повторных процедур, особенно при рецидивах ФП.

Ключевые слова: радиочастотная абляция; фибрилляция предсердий; торакоскопическая абляция; гибридный подход; рецидив фибрилляции предсердий; лечение длительно-персистирующей фибрилляции предсердий.

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BACKGROUND

The development of hybrid surgery for atrial fibrillation (AF) has opened up new prospects for its treatment. Despite the experience gained and increased efficiency, some patients still have refractory and recurrent forms of arrhythmia. Among the modern methods of primary surgery for long-existing AF, MAZE surgeries under cardiopulmonary bypass can be highlighted, including their thoracoscopic variants, and various non-standardized catheter ablation schemes. In recent years, the thoracoscopic MAZE procedure (TM) surgery has gained great popularity in Russia, and the most common method for this approach is the isolation of the pulmonary veins (PVs) with bipolar clamps in combination with the linear effects that isolate the posterior wall of the left atrium — "Dallas lesion set", DLS, and modifications [1, 2]. This study presents the results of reinterventions in patients who initially had exceptionally long-term persistent AF (LPAF) and initially underwent surgery according to the DLS scheme. However, regardless of how AF surgery was started, repeated procedures due to relapse after the primary surgery remain the exclusive prerogatives of catheter techniques. Moreover, only a few studies have focused on specific mechanisms of recurrence after TM surgery [3, 4] and described a few cases. No multicenter studies, long-term follow-ups, and a standard scheme for repeated catheter ablations after DLS surgery have been conducted.

The aim of this study was to establish the structure of arrhythmia recurrence in patients with long-standing persistent AFib after primary epicardial ablation using the Dallas lesion set technique, as well as determining the optimal RFA strategy for recurrence.

MATERIALS AND METHODS

The study included 100 patients with recurrence of various atrial arrhythmias after thoracoscopic ablation (DLS) who underwent surgery in our clinic between 2020 and 2022.

PVs were isolated initially with bipolar clamps, and a monopolar electrode (AtriCure) was used for the lines that isolate the left atrial posterior wall (LAPW). The line along the roof was made after preliminary skeletonization of the atrial wall from fat and fibrous structures, as wide as possible, with special attention to the area closer to the left PV, left atrium (LA) appendage and the exit site of the ligament of Marshall; in addition, the line was expanded along the roof to the aorta. Exit block testing by pacing was not routinely performed. The LA appendage was ligated by the tourniquet technique in all patients [5]. If atrial arrhythmias persisted, cardioversion through the short axis of the heart was performed at the end of the procedure with restoration of sinus rhythm (SR).

Men predominated in this group (68/100). All patients initially had LPAF, and its duration ranged from 1 to 10 years (35.8 ± 10.5 months) before treatment initiation. The LA volume was increased and was 180 ± 48 mL according to computed tomography (CT) findings before epicardial ablation. The left ventricular ejection fraction according to the initial echocardiography (echoCG) was moderately reduced (48 ± 10%).

Catheter ablation was performed depending on the timing of arrhythmia recurrence, ranging from the early postoperative period to 5 years after the primary surgery, with most reinterventions in terms of up to 6 months. In addition to mapping and eliminating the main cause of recurrence, the protocol for endocardial radiofrequency ablation (RFA) included monitoring the isolation of PVs and LAPW.

All patients were informed about the approach of treatment and research and provided informed consent. Not later than 48 h before surgery, all patients underwent transesophageal echoCG or LA CT to rule out thrombosis of the LA appendage and coronary angiography to rule out pathology of the coronary vessels.

Antiarrhythmic and anticoagulant therapy

Postoperative antiarrhythmic therapy (AAT, mainly with amiodarone) after repeated catheter procedures during the first month was performed in all patients. Subsequently, while maintaining SR, AAT was canceled. Before planning endocardial RFA, AAT was canceled, considering the timing of excretion of the drug used. Patients admitted for catheter ablation received anticoagulants continuously without discontinuation in the perioperative period; in the case of warfarin, the international normalized ratio was monitored. During the endocardial procedure, a standard anticoagulation protocol was used (bolus of heparin 100 IU/kg + infusion through transseptal sheath introducers 1,000 IU/h and control of the activated clotting time of >300 s).

Endocardial electrophysiological heart test and radiofrequency ablation

The scenarios for RFA to eliminate the recurrence of arrhythmia were as follows:

1) If atrial arrhythmia (excluding AF) was in progress, mapping and elimination of the mechanism of this arrhythmia were applied;

2) If the procedure was performed in SR (except for paroxysm), an attempt was made to induce arrhythmia;

3) All patients underwent verification (if necessary, additional RFA) of previously performed lines, control of PV and LA posterior wall isolation;

4) If the patient was admitted in AF rhythm (as well as in cases of SR), PV isolation, LAPW isolation, and RFA of the posteroinferior parts of the left atrium were monitored (from the lower line of the LAPW "box" to the coronary sinus (CS) and along the CS, a wide septal line from the mitral valve (MV) to the right superior PV with a branch line to the left superior PV). While AF was maintained, cardioversion was performed. In the case of AF relief in atrial tachycardia or atrial flutter, appropriate ablations were performed until SR

was restored (in some cases, active zones in the right atrium were excluded);

5) In addition, all patients underwent cavotricuspid isthmus (CTI) block.

Of the 138 repeated procedures, 106 were performed on the EnSite Precision navigation system (Abbot Inc.), whereas the remaining 32 procedures were performed on Carto 3 (Biosense-Webster Inc., CA, USA). All patients underwent double transseptal access using unguided introducers. The electrode used for high-density automatic mapping was a multi-pole HD-Greed electrode (Abbot Inc.) and a Lasso electrode (Abbot Inc., Biosense-Webster Inc.), and mapping and ablation were also performed with FlexAbility D, CoolFlex M, and TactiCath (Abbot Inc.) electrodes when using EnSite and a ThermoCool SmartTouch electrode (Biosense-Webster Inc.) for Carto procedures.

Control monitoring in the postoperative period

Patients' condition was monitored during visits to the clinic and through remote monitoring [6]. Cardiac rhythm was assessed 1, 3, 6, 9, and 12 months after RFA according to daily ECG monitoring data or according to the data of implanted devices. Antiarrhythmic therapy was canceled at the first visit 1 month after the endocardial procedure in the absence of sustained atrial arrhythmias.

RESULTS

Between 2020 and 2022, 138 catheter ablation procedures were performed in 100 patients who presented with recurrences of various atrial arrhythmias after TM surgery in the clinic. At the time of writing this article, 34 patients required ⩾ 2 RFAs (2 RFA for 31 patients, 3 RFA for 2 patients, and 4 RFA for 1 patient). In patients with ⩾ 3 RFAs after TM, AF was the recurrent arrhythmia (Fig. 1). The history of the patient with 4 RFAs after TM is described below. The recovery of SR during ablation without defibrillation was associated with a longer arrhythmia-free period in the multiple reintervention group.

Initially, all 100 patients had LPAF. RFA for relapses was performed in terms from early ablations after TM without discharge from the hospital to up to 5 years. More than half of the relapses and repeated RFAs (54/100) occurred in the first 6 months, and in 37 of 54 patients a stable SR was not restored after primary TM before RFA, despite repeated attempts at defibrillation and antiarrhythmic therapy (Fig. 2).

Complications of catheter ablations after TM

Complications of the vascular approach because of unintentional punctures of the arteries such as arteriovenous fistulas were the most common, including two requiring

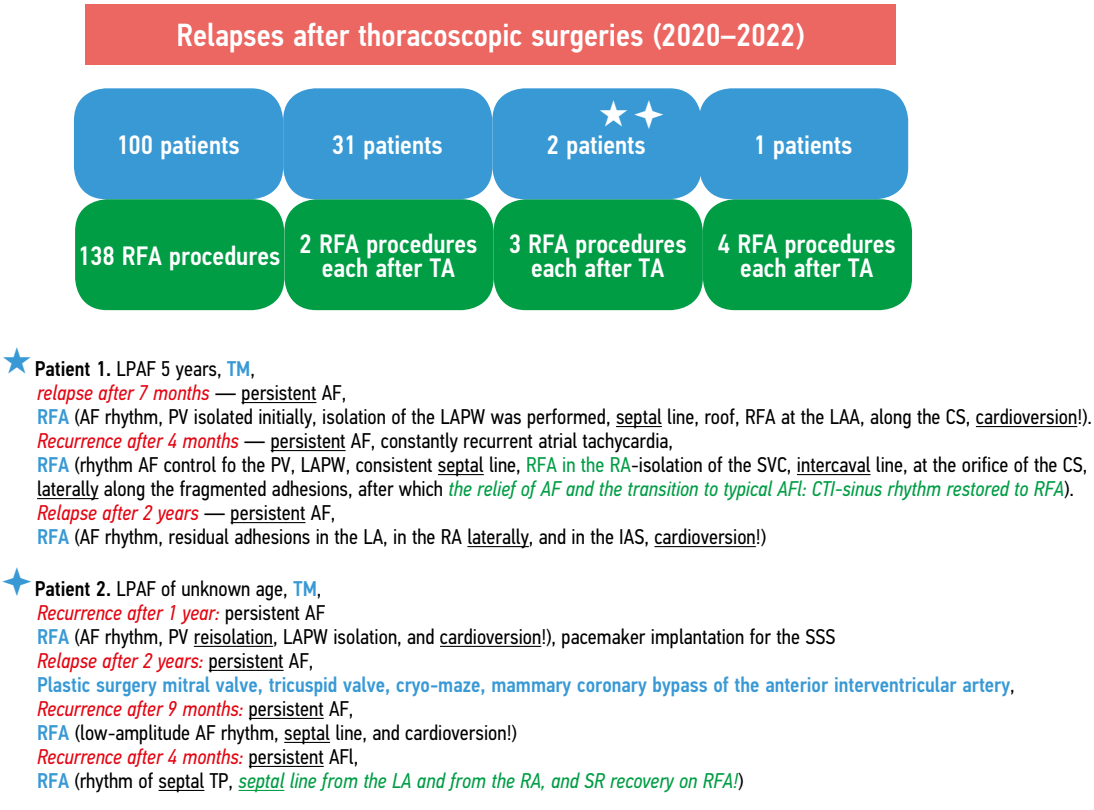

Fig. 1. Patients with recurrent arrhythmias after thoracoscopic surgery: 34 patients had ⩾ 2 RFA after thoracoscopic MAZE surgery (TM) and 2 patients had 3 consecutive radiofrequency ablations (RFA) (described in detail under links). Both patients had atrial fibrillation as the main recurrent arrhythmia. One patient had four RFAs after TM. The restoration of sinus rhythm on RFA was associated with a longer arrhythmia-free period. AFl — atrial flutter; CS — coronary sinus; CTI — cavotricuspid isthmus; IAS — interatrial septum; LAA — left atrial appendage; LAPW — left atrium posterior wall; LPAF — long-term persistent atrial fibrillation; PV — pulmonary veins; RA — right atrium; SR — sinus rhythm; SSS — sick sinus syndrome; SVC — superior vena cava; TA — thoracoscopic ablation

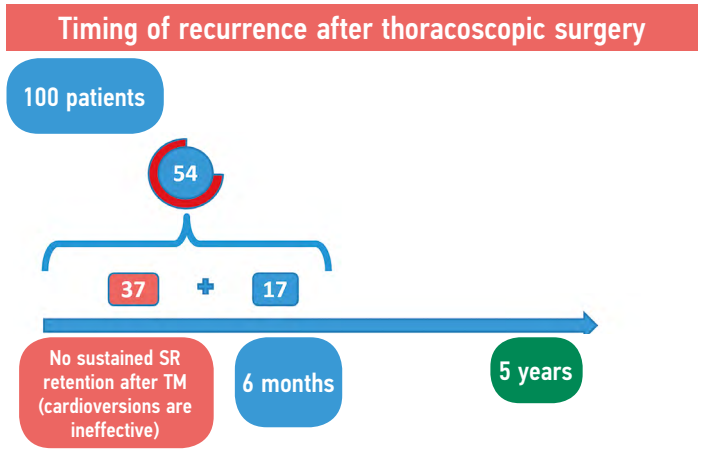

Fig. 2. Timing of the recurrence of arrhythmias after TM. A total of 100 patients (for several cases radiofrequency ablations after TM, the time of the first recurrence is presented in the scheme). During the first 6 months, 54/100 recurrences had occurred, 37 of them had not maintained a stable sinus rhythm after TM, despite repeated attempts at defibrillation. SR — sinus rhythm; TM — thoracoscopic MAZE surgery

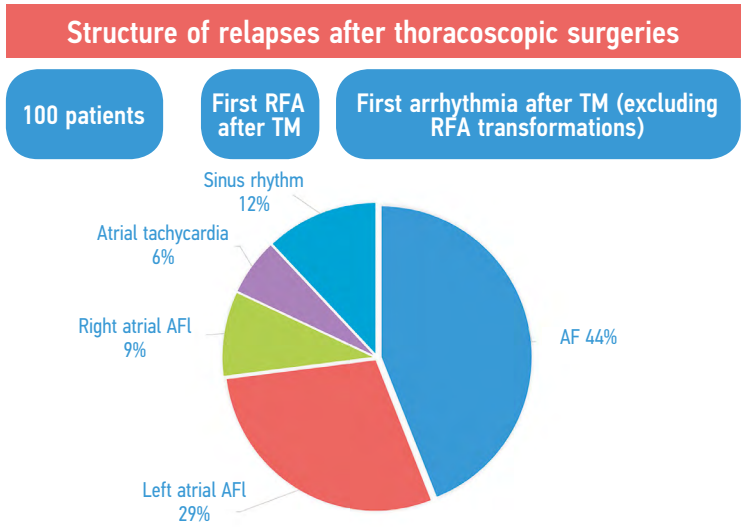

Fig. 3. Structure of relapses during the first radiofrequency ablations after TM. Data on the first rhythm disturbance are presented without taking into account transformations during ablation. "Sinus rhythm" in the diagram means that the patient had sinus rhythm at the start of the radiofrequency ablations procedure and underwent induction, or the standard anatomical ablation scheme after TM (described in the "Materials and Methods"). AF — atrial fibrillation; AFl — atrial flutter; SR — sinus rhythm; TM — thoracoscopic MAZE surgery

surgical treatment. In three patients, control radiography in the early postoperative period revealed paresis of the right phrenic nerve (after ablations in the right atrium and isolation of the superior vena cava — SVC); it was asymptomatic and resolved conservatively. In these patients, no hemopericardium or tamponade occurred. However, one case of bilateral hemothorax developed intraoperatively (perforation of the LA roof with an ablation electrode during RFA of continuous recurrent atrial tachycardia in the early period after TM) [7].

Electrophysiological results

At the start of the initial RFA after TM, 44 patients had AF rhythm, 29 had a LA flutter rhythm with a stable cycle, 12 were admitted with SR (documented paroxysmal arrhythmias), 9 had a typical right atrial flutter rhythm, and 6 had focal continuously recurrent atrial tachycardia (Fig. 3).

Patients without recovery of SR after TM were of particular interest (n = 37). The structure of rhythm disorders in this group is presented in Fig. 4. Non-isolated PVs were registered in these patients atypically frequently for RFA after TM (6/37), particularly in cases of left PV collectors, and LAPW isolation was consistent in only one case (1/37). The total number of arrhythmias significantly exceeded the number of patients (46 types of atrial arrhythmias per 37 patients) due to transformations during ablation or re-induction of different atrial arrhythmias in one procedure. Persistent AF and LA flutter were the most frequent among rhythm disorders, and 8 out of 37 patients had continuously recurrent atrial tachycardias (localizations are detailed in Fig. 4). All 37 patients restored intraoperatively a stable SR as a result of RFA, which was not obtained as a result of TM.

The analysis of amplitude maps after TM, plotted by high-density mapping before RFA, confirms in numerous

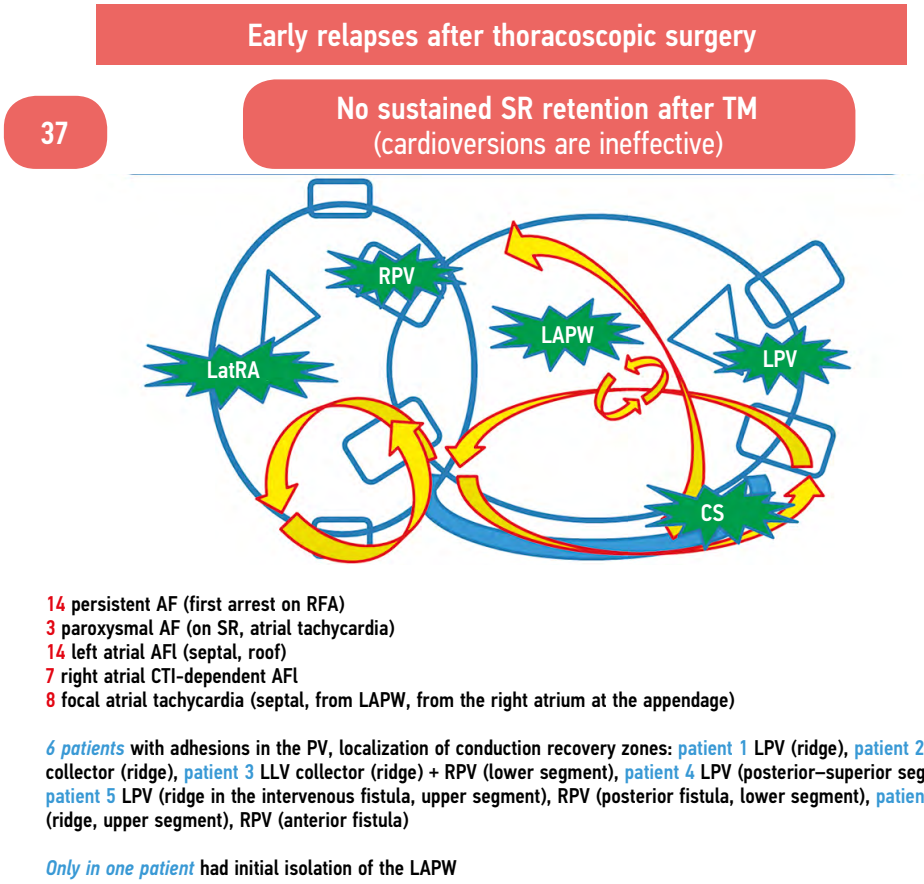

Fig. 4. Results of radiofrequency ablation (RFA) of patients whose TM did not lead to the restoration of a stable sinus rhythm. In this group, non-isolated pulmonary veins were more common, which is generally not typical for patients after TM. AF — atrial fibrillation; AFl — atrial flutter; CS — coronary sinus; CTI — cavotricuspid isthmus; LAPW — left atrium posterior wall; LatRA — lateral segments of the right atrium; LPV — left pulmonary veins; RPV — right pulmonary veins; SR — sinus rhythm; TM — thoracoscopic variant of MAZE surgery

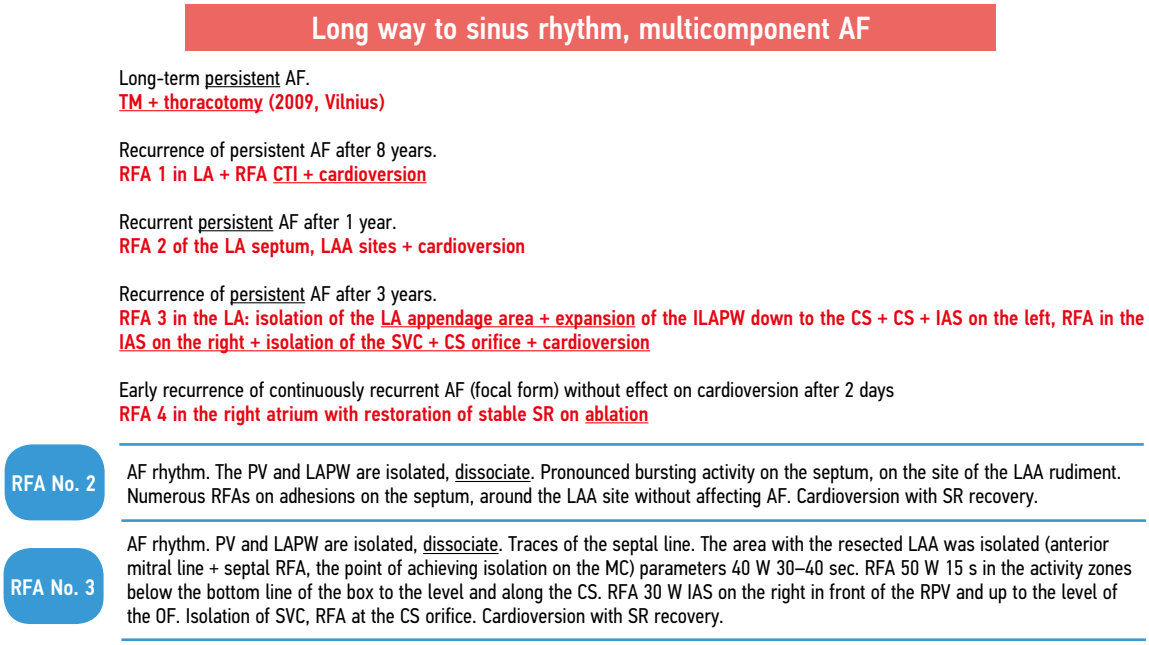

Fig. 5. Multiple radiofrequency ablation (RFA) after TM in the treatment of long-term persistent AF. AF — atrial fibrillation; AFl — atrial flutter; CS — coronary sinus; CTI — cavotricuspid isthmus; IAS— interatrial septum; ILAPW — isolation of the left atrium posterior wall; LA — left atrium; LAA — left atrial appendage; OF — oval fossa; RA — right atrium; RPV — right pulmonary veins; SR — sinus rhythm; SVC — superior vena cava; TM — thoracoscopic MAZE surgery

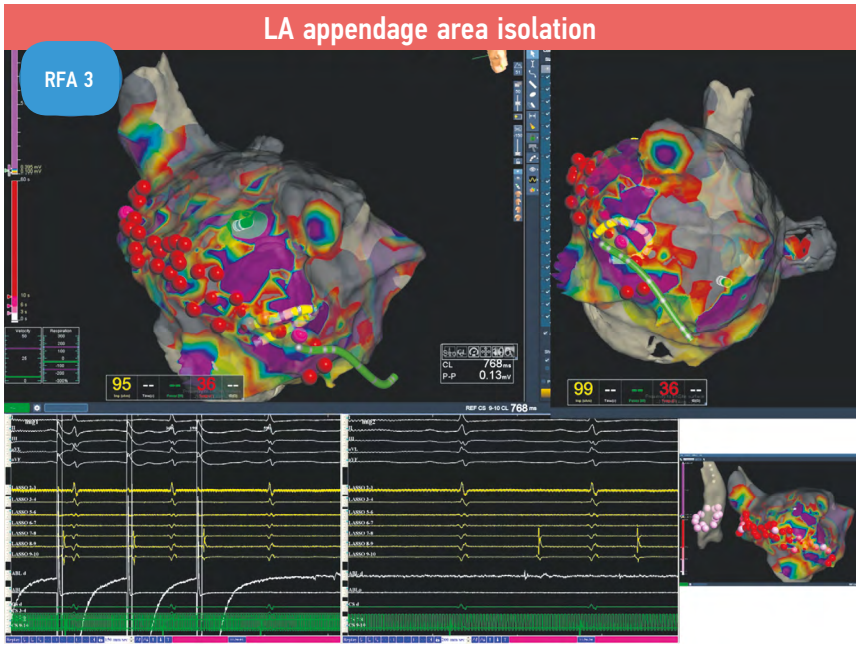

Fig. 6. Multiple radiofrequency ablations (RFA) after thoracoscopic MAZE surgery in the treatment of long-term persistent atrial fibrillation. History of patient A. RFA 3. Stimulation from an ablation electrode with dissociated local capture of the site of the rudiment of the left atrial appendage and spontaneous activity within the blocked zone. Ablation points of the mitral line and on the septum on the right are hidden. LA — left atrium

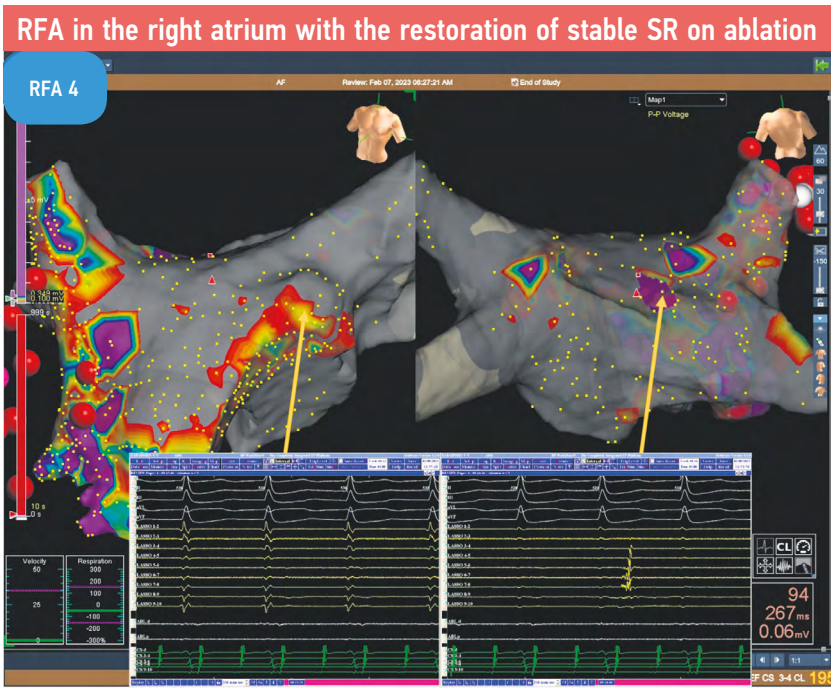

Fig. 7. Multiple radiofrequency ablations (RFA) after thoracoscopic MAZE surgery in the treatment of long-term persistent atrial fibrillation. History of patient A. RFA 4. Left atrial control. Persistent isolation of the left atrial appendage rudiment site with spontaneous dissociated activity. Purple areas on the posterior wall of the left atrium indicate dissociated activity of the block of pulmonary veins – posterior wall of the left atrium

patients the weak points of TM that we have previously described [7, 8]. A typical zone of residual conduction of signals on the LAPW after TM was the bottom line at the right inferior PV and LA roof. A typical cycle of LA flutter is perimitral and septal re-entries caused by the formation of an inhomogeneous cicatricial field not reaching the MV annulus following TM.

The experience of repeated RFAs at intervals of several years until an arrhythmia-free condition was achieved indicated understanding of the mechanisms of maintenance and recurrence of LPAF. In this group, a patient underwent four RFAs after TM (Fig. 5–8). His story sheds light on the causes of the lack of efficiency of existing methods of LPAF surgery and should be described in detail.

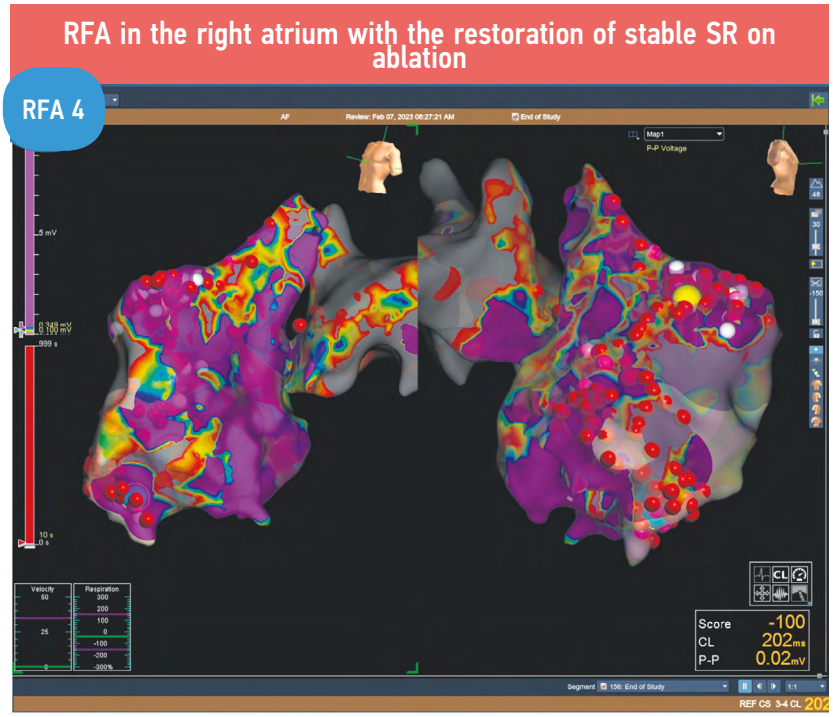

Fig. 8. Multiple radiofrequency ablations (RFA) after thoracoscopic MAZE surgery in the treatment of long-term persistent atrial fibrillation. History of patient A. RFA 4. Amplitude map of the right atrium is presented at the end of the surgery. On the yellow dot at the base of the right atrial appendage, there is cycle switching of atrial tachycardia, and the restoration of sinus rhythm is on the blue dot

The treatment of long-term AF of unknown duration in patient A started with TM in 2009. After 8 years with a recurrence of persistent AF, he visited our center. In 2018, RFA 1 was performed, namely, in the left atrium, and a consistent LAPW isolation with PVs was confirmed (activity dissociates). An additional CTI block and electrical impulse therapy with SR recovery were performed. Persistent AF recurred after 1 year; therefore, RFA 2 was performed, where pronounced burst activity was detected on the interatrial septum and area of the rudiment of the LA appendage. RFA in these areas did not lead to AF relief; again, SR was restored by electrical impulse therapy (EIT), and CTI block was confirmed in SR. The normal rhythm lasted for 3 years after these interventions. RFA 3 for a recurrence of persistent AF was performed in the scope of mitral block in the left atrium + septal line with the achievement of isolation of the LA appendage rudiment (dissociating activity), expansion of RFA from the LAPW down to the level of the CS, along the CS. In RFA 3, work was started in the right atrium with ablation of the interatrial septum to the right of the level of projection of the right PVs up to the oval fossa + isolation of the SVC + ablation of the CS orifice. Despite the large amount of RFA, EIT was again required to stop AF. On day 2 after RFA 3, arrhythmias recurred early, but in the form of continuously recurrent focal tachycardia, turning into AF. After 3 months, the patient was admitted for RFA 4, where at the start of the surgery in the left atrium, complete isolation of the block PV – LAPW + LA appendage site was confirmed (activity dissociates), and RFA was then performed in the right atrium. At RFA 4, the patient no longer had AF, and regular tachycardia was recorded with a cycle of 250 ms. After RFA at the base of the right atrial appendage, the rhythm transformed into atrial tachycardia with a cycle of 270 ms, which was stopped by RFA in the lower lateral parts of the right atrium. Areas with activity much faster than the tachycardia cycle were found in the right atrium, and the activity in them gradually slowed down and stopped during RFA (Fig. 9). After the restoration of a stable SR, these zones demonstrated dissociating isolated bursts (Fig. 10), similar to those recorded on the LAPW and LA appendage area. This finding indicates the existence of areas of burst activity that can act as potential triggers for AF not only in the LA but also, as in the patient presented, in the right atrium. Until all such areas are isolated, arrhythmia recurs. After recovery of SR in RFA 4, the patient is under close follow-up. Data on arrhythmias were not received during the year.

DISCUSSION OF THE RESULTS

In recent years, the development of hybrid surgery has led to the accumulation of experience in repeated catheter interventions. However, only a few studies were conducted, and the number of cases described is not large. When RFA was performed regardless of arrhythmia recurrence, it is often referred to as a planned-implemented hybrid approach. Patients in nearly all studies are heterogeneous and include both paroxysmal and LPAF [9–11]. All these factors lead to scattered data on the causes of relapse of arrhythmias. In this study, only patients with a recurrence of arrhythmias

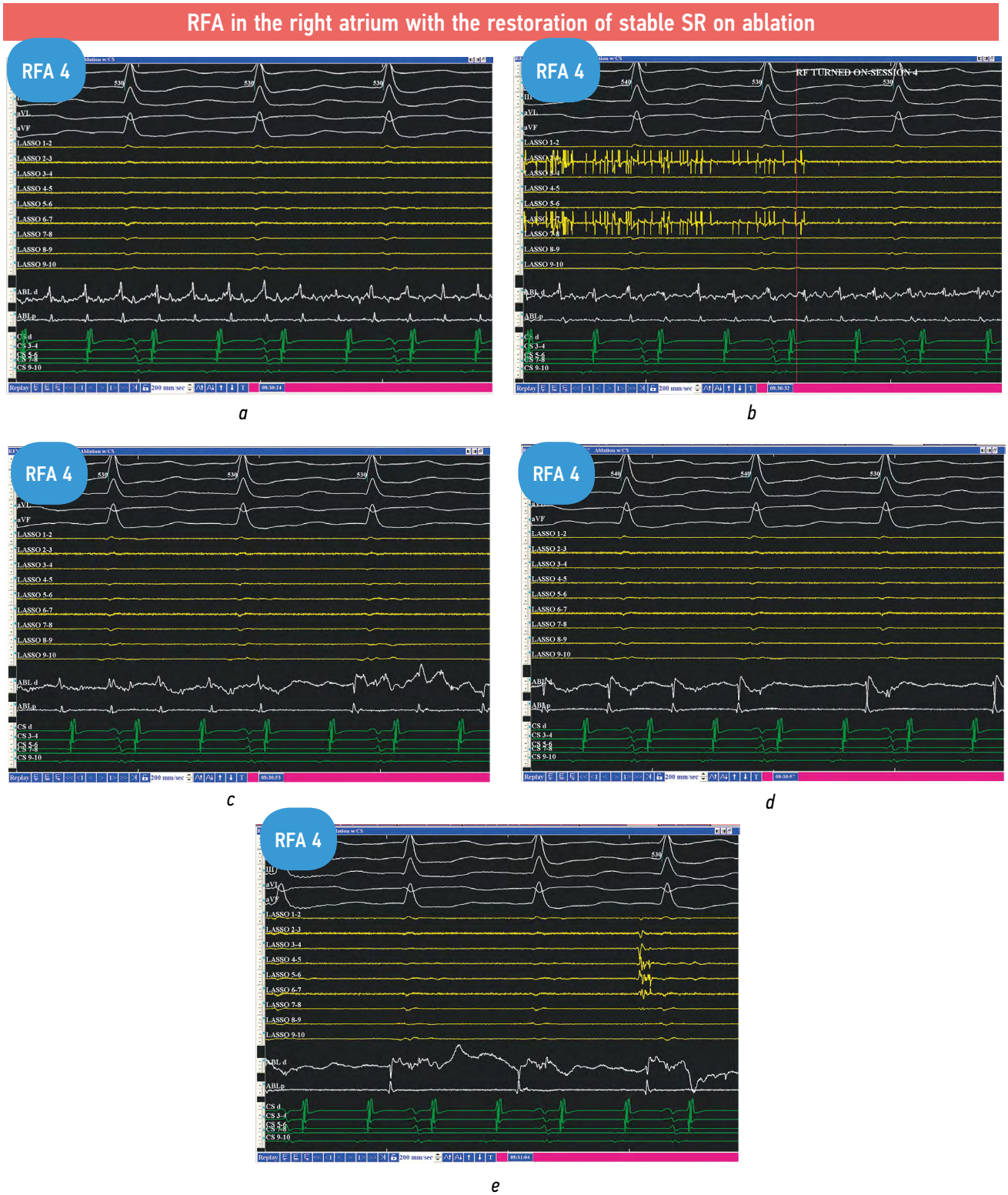

Fig. 9. Multiple radiofrequency ablations (RFA) after thoracoscopic MAZE surgery in the treatment of long-term persistent atrial fibrillation. History of patient A. RFA 4. Active area in the right atrium (a series of images in chronological order, reflecting the change in the activity of the arrhythmogenic zone under the influence of ablation: *a* — frequent bursting activity before the start of RFA; *b–d* — slowing of the cycle and arrest of spontaneous activity during RFA; *e* — rhythm of this area after RFA)

after TM surgery using the DLS method were included. They initially had a LPAF. In our earlier study [7], the main aspects and "weak points" of epicardial ablation were already described, namely, the application of lines with a monopolar electrode does not guarantee the transmurality of damage; as a result, a potentially arrhythmogenic inhomogeneous scar is formed. When the line expands to the aorta, an area of intact myocardium is preserved between the cicatricial

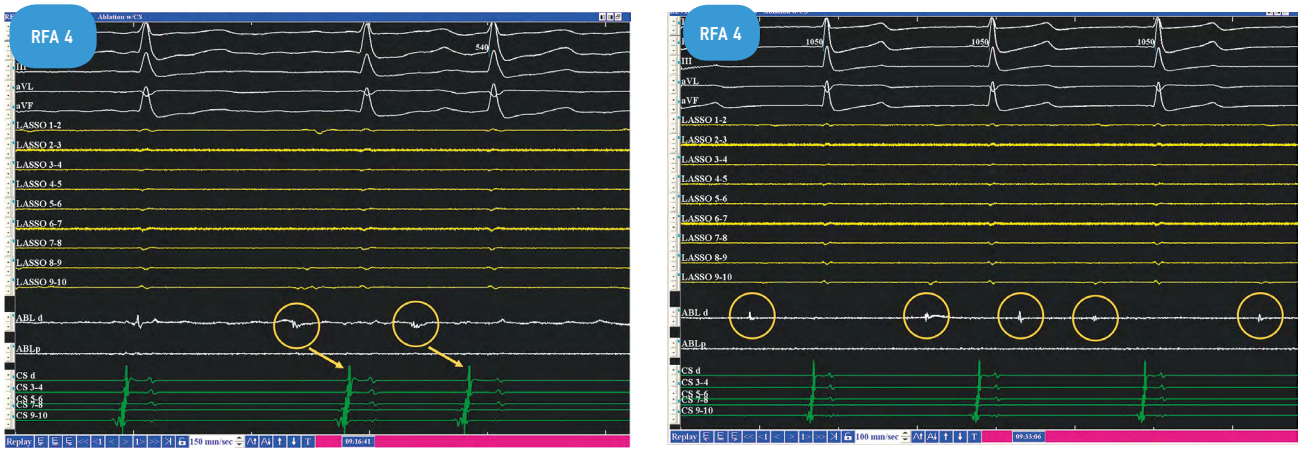

Fig. 10. Multiple radiofrequency ablations (RFA) after thoracoscopic MAZE surgery in the treatment of long-term persistent atrial fibrillation. History of patient A. RFA 4. *a* — spontaneous activity of a non-isolated area in the right atrium after the restoration of sinus rhythm; *b* — dissociating spontaneous bursting activity of an isolated area in the right atrium in the presence of sinus rhythm

field and the annulus fibrosis of the MV, which creates a substrate for perimitral flutter. The technique advantage is bipolar ablation of the PVs, which allows almost guaranteed isolation of all PVs. In addition to the restoration of LAPW conduction, focal atrial tachycardias of various localizations can cause the relapse. Further study of these patients in this trial confirms the aspects already described in numerous cases. These are data of long-term monitoring and multiple repeated procedures for the recurrence of arrhythmias, which demonstrates clearly the multicomponent nature of LPAF. All mechanisms of recurrence after TM surgery can be divided into two groups, namely (1) an arrhythmogenic substrate formed as a result of the primary surgery and (2) individual mechanisms of AF, which remained beyond previous ablations. If the first reason is stereotyped and determined, initially, by the peculiarities of the epicardial ablation technique, then the need arises for a stereotypical set of catheter RF effects that eliminate all potentially arrhythmogenic consequences of TM during the repeated procedures. Such intervention should include control and reisolation of the PVs, control and reisolation of the LA posterior wall, septal line from the MV to the right superior PV with a Y-shaped branch to the left superior PV, and CTI block. This RFA set will eliminate and prevent future potential incisional arrhythmias in fragmentary scars after TM. Performing it immediately at the initial RFA in the case of relapse will serve as electrophysiologically substantiated prevention of relapses. The second reason for repeated procedures, individual mechanisms of AF, not affected by the previous surgery, is less standardized and includes atrial tachycardias of unpredictable localizations (often several mechanisms in one patient), which requires in each case a different set of extensive ablations in both the left and right atrium to eliminate all active zones that support and trigger AF.

CONCLUSIONS

The study revealed that after TM surgery (according to the DLS method), relapses, return of AF, and incisional arrhythmias are predominant. In addition to the correction of the underlying cause of arrhythmia recurrence, epicardial ablation creates a potentially arrhythmogenic substrate that must be eliminated by catheter RFA. AF recurrence represents the most difficult cases. The restoration of SR in recurrent AF after TM is possible but may require extensive RFA in both atria as a result of repeated procedures until all potential AF mechanisms present in a patient have been eliminated.

ADDITIONAL INFORMATION

Competing interests. The authors declare that they have no competing interests.

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Research Article

New-onset atrial fibrillation in patients with SARS-CoV-2 pneumonia as a manifestation of acute myocardial injury

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BACKGROUND: Over the past 3 years, the prevalence of atrial fibrillation (AF) has increased significantly worldwide, which was associated with the pandemic caused by SARS-CoV-2. It is accompanied by an increase in the cases of ischemic stroke, myocardial infarction, and development of heart failure due to acute myocardial injury. Given the high lethality of SARS-CoV-2 infection (COVID-19), studying the characteristics of new-onset AF is essential.

AIM: The study aims at determining the predictors of new-onset AF in patients with COVID-19 pneumonia and at analyzing the clinical and pathophysiological characteristics of acute myocardial injury.

MATERIALS AND METHODS: In 36 patients aged 44–82 years (average 68.0) with COVID-19 pneumonia, AF paroxysms were recorded for the first time. All of them underwent computed tomography of the chest, electrocardiography, and echocardiography. The left ventricular ejection fraction was calculated using the Simpson method. Oxygen saturation was determined as blood oxygen saturation. Clinical blood tests were performed, C-reactive protein (CRP), ferritin, D-dimer, fibrinogen, and troponin I levels were measured.

RESULTS: Along with the well-known predictors of AF development (arterial hypertension, coronary heart disease, left ventricular myocardial hypertrophy, and left atrial dilatation), with COVID-19 pneumonia, new-onset AF paroxysms were recorded in patients of the middle, elderly, and late-life age. In 44.4% of patients with AF, cardiomegaly occurred with dilatation of both atria and ventricles. With decreased left ventricular ejection fraction, the incidence of AF paroxysms reached 61.5%. With preserved ejection fraction, AF paroxysms occurred much less frequently (27%). In patients with AF, the extent of lung damage is on average 62.5% (20–80%) with oxygen support saturation of 93% (76–97%). Serum troponin I levels of > 2000 ng/L indicated acute myocardial injury. CRP and blood ferritin values confirmed the presence of a pronounced inflammatory component in myocardial injury. High concentrations of blood fibrinogen and D-dimer, reaching 16,301 ng/mL, were associated with a tendency to hypercoagulation in patients with AF and COVID-19 pneumonia.

CONCLUSIONS: COVID-19 has a direct damaging effect on the myocardium and probably persists for a long time, which may induce AF in patients with acute pneumonia.

Keywords: atrial fibrillation; SARS-CoV-2; predictors.

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Научная статья

Впервые возникшая фибрилляция предсердий у пациентов с SARS-CoV-2-пневмонией как манифестация острого повреждения миокарда

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Актуальность. За последние три года в мире существенно выросла распространенность фибрилляции предсердий (ФП), что связывают с пандемией, вызванной вирусом SARS-CoV-2. Это сопровождается увеличением количества ишемических инсультов, инфарктов миокарда, развитием сердечной недостаточности вследствие острого повреждения миокарда. В связи с высокой летальностью пациентов, инфицированных SARS-CoV-2, изучение особенностей впервые возникшей ФП является крайне необходимым.

Цель — определить предикторы впервые возникшей ФП у пациентов с SARS-CoV-2-пневмонией, изучить клинические и патофизиологические особенности острого повреждения миокарда.

Материалы и методы. У 36 пациентов в возрасте 44–82 лет (в среднем 68,0 года) с SARS-CoV-2-ассоциированной пневмонией впервые были зафиксированы пароксизмы ФП. Всем выполнялась компьютерная томография грудной клетки, электрокардиографическое, эхокардиографическое обследование; расчет фракции выброса левого желудочка (ФВ ЛЖ) проводили по методу Симпсона. Определяли сатурацию (SpO_2) — насыщение крови кислородом, клинический анализ крови, С-реактивный белок (СРБ), ферритин, Д-димер, фибриноген, тропонин I.

Результаты. Было показано, что наряду с общеизвестными предикторами развития ФП (артериальная гипертензия, ишемическая болезнь сердца, гипертрофия миокарда ЛЖ, расширение левого предсердия) при SARS-CoV-2-пневмонии впервые возникшие пароксизмы ФП регистрировались у пациентов среднего, пожилого и старческого возраста. У 44,4 % пациентов с ФП имела место кардиомегалия с дилатацией обоих предсердий и желудочков и снижением фракции выброса левого желудочка, при этом частота пароксизмов ФП достигала 61,5 %; при сохраненной фракции выброса пароксизмы ФП развивались значительно реже — в 27 % случаев. Установлено, что у пациентов с ФП объем поражения легких составляет в среднем 62,5 % (20–80 %) при сатурации на кислородной поддержке 93 % (76–97 %). Об остром повреждении миокарда свидетельствовали уровни тропонина I в сыворотке крови, превышающие отметку в 2000 нг/л. Показатели СРБ и ферритина крови подтверждали наличие выраженного воспалительного компонента при повреждении миокарда. Высокие концентрации фибриногена крови и Д-димера, достигающие 16301 нг/мл, ассоциировались с наклонностью к гиперкоагуляции у пациентов с ФП на фоне SARS-CoV-2-пневмонии.

Заключение. Коронавирус SARS-CoV-2 оказывает прямое повреждающее воздействие на миокард и, вероятно, длительно персистирует, что может быть причиной развития ФП у больных острой формой пневмонии.

Ключевые слова: фибрилляция предсердий; SARS-CoV-2; предикторы.

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ЭКО•ВЕКТОР

BACKGROUND

At the turn of the 20th – 21st centuries, an emergence of a pandemic of any infection could not be supposed. All pandemics seemed to become history. It was speculated that vaccinating the general population, using high-tech diagnostic methods, and prescribing new anti-infective drugs could reliably protect everyone. The Spanish influenza epidemic was probably the last largest one in Europe. In 1918–1919, over 18 months, more than 550 million people, or 29.5% of the global population, fell ill. Moreover, 50–100 million people died from it, which was 2.7–5.3% of the number of cases. In the Russian Soviet Federative Socialist Republic, approximately 3 million people died from the Spanish influenza, and this amounted to 3.4% of the country's total population [1].

In December 2019, an outbreak of pneumonia of unknown etiology was registered among residents of Wuhan City, China. The study of bronchoalveolar secretions and blood samples of patients identified the pathogen as an RNA-containing coronavirus (SARS-CoV-2). The disease was named Coronavirus disease-19 (COVID-19). In March 2020, the World Health Organization declared COVID-19 a pandemic. As of May 2023, more than 765 million people had COVID-19, and nearly 7 million died, globally.

Having quickly recovered from the first shock caused by high mortality rates, the entire global medical community started to investigate the new disease. Thus, in a comprehensive analysis of 700 autopsies of patients who died from this new coronavirus infection, Rybakova et al. (2020) established that in 43% of cases, COVID-19 was the only underlying cause of death. The major thanatogenetic mechanisms in COVID-19 were acute respiratory, pulmonary heart failure (HF) and multiple organ dysfunction. The most common comorbid pathology in patients with COVID-19 included cardiovascular diseases, diabetes mellitus, and obesity [2].

Katsoularis et al. (2021) analyzed 86,742 COVID cases in Sweden. They compared the obtained results with the incidence of myocardial infarction (MI) and ischemic strokes in 348.481 patients in the control group. They concluded that MI and ischemic stroke were part of the clinical presentation of COVID-19, and their risk remained significantly increased during the first 2 weeks after recovery [3].

Cardiac arrhythmias occur in 19–21% of patients with severe COVID-19 [4, 5], whereas the incidence of new-onset AF in patients with COVID-19 varies from 3.6% to 6.7% [6, 7]. Thus, in the study by Bhatia et al. (2021), who analyzed 644 patients with severe COVID-19, AF episodes on electrocardiography (ECG) were recorded for the first time in 3.6% of cases [8]. In a meta-analysis, Romiti et al. (2021) examined 187.716 patients with COVID-19 and revealed that the prevalence of AF with COVID-19 was approximately two times higher than in the general population [9].

According to Rosenblatt et al. (2022), 27.851 of 30.999 patients hospitalized with COVID-19 had no AF history. In 1517 (5.4%) patients atrial fibrillation developed for the first time during their COVID-19 course. The presence of AF was associated with higher rates of overall mortality (45.2% versus 11.9%) and mortality due to MI, stroke, cardiogenic shock, and HF (23.8% versus 6.5%) [10].

Wollborn et al. (2022) compared the incidence of AF in 5005 patients from the pre-pandemic cohort and 2283 patients with COVID-19. They found that the incidence of AF was 1.57 times higher in the COVID-19 group than in the pre-pandemic group [11].

The aim of the study was to identifying predictors of new-onset AF in patients with COVID-19 pneumonia as well as at determining the clinical and pathophysiological characteristics of acute myocardial injury (AMI).

MATERIALS AND METHODS

This controlled nonrandomized cohort study enrolled 216 patients aged 23-82 years with PCR-diagnosed COVID-19 pneumonia. All patients were hospitalized in the acute period of the disease, i.e., on days 2–7 (average 5.2). Of these, 32 patients aged 52–86 (mean 78.6) years died from severe bilateral viral pneumonia on days 6–10 of the hospital stay. 30 patients with paroxysmal AF that occurred before COVID-19 diagnoses were excluded from the sample.

In 36 patients (group I) aged 44–82 years (average, 68 years, Table 1) with COVID-19 pneumonia, AF paroxysms were recorded for the first time during the hospital stay. The duration of the attacks ranged from 35 s to 3 min. In these patients, 2 paroxysms were recorded in 2 patients with CT1, 30 in 22 patients with CT2, 16 in 10 patients with CT3, and 6 in 2 patients with CT4, which totaled 54 paroxysms.

All patients had arterial hypertension (AH), and 23 of 36 patients (63.9%) had a history of coronary heart disease (CHD), including 8 patients with MI. Out of 36 patients, 7 (19.4%) had diabetes mellitus type II (DM2), and the body mass index (BMI) was 33.1 (22–43) kg/m^2.

Moreover, 64 patients with COVID-19 pneumonia without AF paroxysms constituted the control group (group II). The age of the patients ranged from 23 to 64 years, with a mean of 41 years. Group I patients were older than group II patients (p = 0.0036), and they significantly more often experienced CHD, AH, and DM2. In group II, AH was determined in 20 of 64 patients (31.2%), CHD was registered in 3 patients (4.7%), and DM2 was noted in 3 patients (4.7%). BMI was 26,9 (18–36) kg/m^2, which was significantly lower than in group I (p = 0.0458).

Echocardiography (echoCG) was performed on Philips EnVisor (Philips Electronics N.V.) and Toshiba Artida (Toshiba Medical Systems) devices on day 1 of the hospital stay. The study was performed according to the standard method using B and M scanning modes, as well as pulsed-wave, and continuous-wave modes. Left ventricular ejection fraction (LVEF) was calculated using the Simpson method.

HF with preserved EF (⩾ 50%), HF with moderately reduced EF (40–49%), and HF with low EF (< 40%) were identified.

In all patients, cardiospecific enzyme troponin I, C-reactive protein (CRP), ferritin, D-dimer, fibrinogen, and creatinine levels were determined, and clinical blood test was performed in the clinical laboratory of St. Petersburg City Hospital Pokrovskaya.

Statistical analysis was performed using the non-parametric Mann–Whitney test. A p-value < 0.05 was considered significant. Spearman's coefficient was applied

Table 1. Clinical characteristics of the patients

Parameters	Atrial fibrillation patients, Group I, *Me* (IQR)	*n* = 36	Patients without atrial fibrillation, Group II, *Me* (IQR)	*n* = 64	*p*
Age, years	68 (44–82)	–	57 (23–64)	–	0.0036
⩽ 44	44	1	38 (35–43)	29	–
45–59	57 (46–59)	10	47 (45–54)	17	0.043
60–74	70 (65–74)	17	61 (60–68)	18	0.038
75–89	82 (75–82)	8	–	–	–
Sex, M/F, *n*	20/16	–	40/24	–	–
Body mass index, kg/m^2	33.1 (22–43)	36	26.9 (18–36)	64	0.0458
Coronary heart disease	63.9%	23	4.7%	3	0.0001
History of MI	22.2%	8	3.1%	2	0.0002
Arterial hypertension	100%	36	31.2%	20	0.0001
Diabetes mellitus	19.4%	7	4.7%	3	0.0283
CT (%)	41 (20–80)	36	33 (10–79)	64	0.0361
CT1 (%)	23 (20–25)	6	16 (10–24)	37	0.0035
CT2 (%)	40 (30–49)	15	29 (27–45)	17	0.0471
CT3 (%)	59 (52–74)	11	51 (50–61)	7	0.0346
CT4 (%)	79 (75–80)	4	77 (75–79)	3	0.0381
Saturation (SpO_2) (%)	91 (76–97)	–	96 (84–98)	–	0.0001

Note. *n,* number of patients; grade I respiratory failure (RF), SpO_2 of 90-94%; grade II RF, SpO_2 of 75–89%; grade III RF, SpO_2 < 75%; normal saturation index, ⩾ 95%; CT, volume of lung tissue damage; CT1, < 25% of damage; CT2, 25–49% of damage; CT3, 50–75% of damage; CT4, > 75% of damage.

Table 2. Biochemical parameters of the blood in patients examined

Parameters	Atrial fibrillation patients, Group I (*n* = 36), *Me* (IQR)	Patients without atrial fibrillation, Group II (*n* = 64), *Me* (IQR)	*p*
CRP, mg/L norm 0–5	77.4 (30.5–189)	44.7 (9.1–167)	0.0027
Ferritin, μg/L norm 20–250	723.5 (85–3500)	577.4 (56–1104)	0.0349
Troponin I, ng/L norm 0–34.2	289.6 (5.9–2041)	29.4 (2.8–165)	0.0027
D–dimer, ng/mL norm 0–230	2040 (321–16301)	494.6 (125–3831)	0.0001
Fibrinogen, g/L, norm 2–4	5.8 (3.6–8.3)	5.2 (3.4–7.9)	0.048
Creatinine, μmol/L, norm 44–110	116.4 (63–234)	96.1 (55–197)	0.062
Leukocytes, 10^9/L	7.5 (4.0–13.3)	7.9 (3.5–20.1)	0.065
Lymphocytes, n	1.15 (0.8–3.0)	1.3 (0.9–2.8)	0.073
Platelets, 10^9/L	269.4 (50–453)	244.4 (83–411)	0.093
Erythrocytes, 10^{12}/L	4.3 (3.2–5.8)	4.7 (3.6–5.8)	0.084

for the correlation analysis of relationships between the analyzed parameters.

RESULTS

Chest CT revealed that the extent of lung tissue damage in group I was on average 41% (20–80%), which was significantly higher than that in group II, with 33% (10–79%) (p = 0.0361). Moreover, group I recorded the following extent of lung damage: CT1 (p = 0.0035), CT2 (p = 0.0471), CT3 (p = 0.0346), and CT4 (p = 0.0381).

The average oxygen saturation in the air upon hospital admission was significantly lower in patients with diagnosed AF paroxysms with 93% (76–97%) than in the comparison group with 96% (84–98%) (p = 0.0001). Biochemical blood parameters are presented in Table 2.

On analysis of biochemical blood test data, the patients with AF showed higher concentrations of CRP (p = 0.0027), ferritin (p = 0.0349), D-dimer (p = 0.0001), fibrinogen (p = 0.048), and troponin I (p = 0.0027).

An increased risk of thrombogenesis and a higher procoagulatory activity of the hemostasis system in group I, compared to group II, was evidenced by fibrinogen and D-dimer values. This was also confirmed by the low platelet count in groups I (50×10^9/L) and II (83×10^9/L).

The level of troponin I, which indicates the AMI level, was 9.8-12.4 times higher in group I than in group II. No significant difference in blood creatinine levels was found. The severity of COVID-19 was indicated by low lymphocyte counts (1.15 (0.8–3.0) in group I and 1.3 (0.9–2.8) in group II; p = 0.073), which is typical of COVID-19. No significant difference in leukocyte and erythrocyte counts was noted.

EchoCG parameters of patients with LVEF of ⩾50% are presented in Table 3. When comparing echoCG in patients with LVEF of ⩾ 50%, group I had higher LV myocardial mass indices (MMI) (p = 0.032) and left atrial volume index (LAVI) (p = 0.034) than group II. The LV end-diastolic volume indices (EDVI) did not exceed the norm in all patients; however, they were higher in group I than in group II (p = 0.047). In addition, patients with AF were older (p = 0.047).

All patients with LVEF of 40-49% had an increase in LV MMI and LAVI; however, group I had higher values for both LV MMI (p = 0.021) and LAVI (p = 0.003). Group I had higher LV EDVI than group II (p = 0.035). Group I patients were older (62 (55-77) years) than group II years (54 (51–60) years) (p = 0.028) (Table 4).

EchoCG data in patients with LVEF < 40% are presented in Table 5. In group I with LVEF < 40%, all echoCG parameters exceeded the norm and were significantly higher than those in group II. Thus, the LVMMI reached 201 g/m^2, the EDVI was 82 mL/m^2, and the ESVI reached 41 mL/m^2. Both atria were enlarged (LAVI up to 70 mL/m^2, RAVI up to 32 mL/m^2). The difference with the indicators of group II was highly significant. The age of patients with low LVEF ranged from 59 to 82 years, with an average of 70 years (p = 0.041).

Group 1 turned out to be very heterogeneous (Table 6). Thus, in 16 of 36 patients (44.4%) (group IA) with LVEF < 50%, a

Table 3. EchoCG parameters in patients with left ventricular ejection fraction of ⩾ 50%

Parameters	Atrial fibrillation patients, Group I (n = 20), *Me* (IQR)	Patients without atrial fibrillation, Group II (n = 54), *Me* (IQR)	p
LV MMI, g/m^2	119 (112–132)	107 (94–124)	0.032
EDVI, mL/m^2	48 (38–60)	40 (38–52)	0.047
End-systolic volume index (ESVI), mL/m^2	23 (20–27)	19 (18–23)	0.800
LAVI, mL/m^2	44 (37–51)	31 (24–36)	0.034
Right atrial volume index (RAVI), mL/m^2	23 (18–26)	21 (18–24)	0.230
LVEF, %	59 (52–64)	62 (58–65)	0.068
Age, years	63 (44–79)	43 (35–54)	0.047

Table 4. EchoCG parameters in patients with left ventricular ejection fraction of 40–49%

Parameters	Atrial fibrillation patients, Group I (n = 12), *Me* (IQR)	Patients without atrial fibrillation, Group II (n = 8), *Me* (IQR)	p
LV MMI, g/m^2	135 (128–165)	123 (120–141)	0.021
EDVI, mL/m^2	65 (51–74)	51 (43–56)	0.035
End-systolic volume index (ESVI) , mL/m^2	30 (28–37)	26 (22–28)	0.090
LAVI, mL/m^2	50 (40–56)	41 (38–45)	0.003
Right atrial volume index (RAVI), mL/m^2	26 (24–30)	23 (20–28)	0.090
LVEF, %	44 (41–48)	46 (43–49)	0.044
Age, years	62 (55–77)	54 (51–60)	0.028

Table 5. EchoCG parameters in patients with left ventricular ejection fraction (LVEF) < 40%

Parameters	Atrial fibrillation patients, Group I (*n* = 4), *Me* (IQR)	Patients without atrial fibrillation, Group II (*n* = 2), *Me* (IQR)	*p*
LV MMI, g/m^2	154 (141–201)	141 (132–163)	0.005
EDVI, mL/m^2	77 (68–82)	59 (48–74)	0.021
End-systolic volume index (ESVI), mL/m^2	39 (37–41)	32 (28–36)	0.047
LAVI, mL/m^2	60 (56–70)	49 (43–52)	0.0001
Right atrial volume index (RAVI), mL/m^2	34 (31–37)	30 (24–32)	0.043
LVEF, %	36 (35–38)	38 (37–39)	0.038
Age, years	70 (59–82)	65 (60–68)	0.041

Table 6. Comparative analysis of the biochemical parameters of the blood and echoCG parameters in group I with atrial fibrillation and left ventricular ejection fraction (LVEF) < 50% and ⩾ 50%

Parameters	LVEF < 50%, Group IA (*n* = 16), *Me* (IQR)	LVEF ⩾ 50%, Group IB (*n* = 20), *Me* (IQR)	*p*
MMI, g/m^2	154 (128–201)	119 (112–132)	0.0001
EDVI, mL/m^2	73 (51–82)	48 (38–60)	0.001
End-systolic volume index (ESVI), mL/m^2	34 (28–41)	23 (20–27)	0.001
LAVI, mL/m^2	59 (56–64)	44 (37–51)	0.002
Right atrial volume index (RAVI), mL/m^2	33 (24–37)	23 (18–26)	0.010
LV EF, %	40 (35–48)	59 (52–64)	0.001
CRP, mg/L	116 (57–189)	87 (30,5–127)	0.0001
Ferritin, μg/L	947 (232–3500)	567 (85–1504)	0.002
Troponin I, ng/L	546 (5,9–2041)	114 (14–365)	0.0001
D-dimer, ng/mL	2943 (564–16301)	1246 (375–6031)	0.005
Fibrinogen, g/L	5,8 (5,2–8,3)	4,9 (3,6–6,3)	0.0362
Lymphocytes, n	1,08 (0,8–1,3)	1,3 (1,1–3,0)	0.045
Platelets, 10^9/L	277 (50–453)	185 (95–308)	0.038
Age, years	74 (48–82)	63 (44–79)	0.035

Table 7. Results of the correlation analyses between blood biochemical parameters and echoCG parameters in group IA with atrial fibrillation and left ventricular ejection fraction (LVEF) < 50% (*n* = 16)

Parameters		EF < 50%	EDVI	ESVI	LAVI	RAVI
CRP	*r*	–1.00	0.89	0.83	0.85	0.68
	p	0.0001	0.001	0.002	0.004	0.013
Troponin I	*r*	–0.90	0.79	0.76	0.94	0.65
	p	0.0001	0.008	0.002	0.003	0.001
Ferritin	*r*	–0.89	0.84	0.68	0.61	0.81
	p	0.0001	0.003	0.040	0.046	0.002
Fibrinogen	*r*	–0.63	0.80	0.78	0.70	0.71
	p	0.040	0.0001	0.001	0.002	0.002
D-dimer	*r*	–1.0	0.75	0.65	0.64	0.90
	p	0.0001	0.010	0.040	0.010	0.0001

high LVMMI was noted, and cavities of both atria and ventricles were dilated, as evidenced by the EDVI, end-systolic volume, LA volume, and right atrial volume. This group consisted of patients of middle, elderly, and late-life age.

In 20 of 36 patients (55.6%) (group IB) with LVEF of ⩾50%, the LVMMI moderately increased, and the LAVI increased. The EDVI, ESVI, and RAVI were normal, and the difference with group IA was highly significant. Group IB patients were somewhat younger than group IA patients ($p = 0.035$).

Compared to group IB, group IA had significantly higher indicators of the general inflammatory response (CRP and ferritin), procoagulatory activity of the blood (D-dimer and fibrinogen), and AMI level (troponin I). Thus, the CRP level was 1.3–1.5 times higher, ferritin level 1.7–2.3 times higher, D-dimer level 2.4–2.7 times higher, fibrinogen level 1.2 times higher, and troponin I level 4.8–5.6 times higher. Moreover, the blood lymphocytes level was 1.2–2.3 times lower than in group IB, which indicated a more severe viral infection. Indeed, according to CT data, the extent of lung tissue damage reached 62.5% (20–80%) in group IA compared to 43.5% (20–70%) in group IB ($p = 0.0001$). This was accompanied by lower oxygen saturation values, i.e., 92% (76–97%) and 94% (84–97%) ($p = 0.0001$), respectively.

Spearman's rank correlation was used to assess the complex effect of inflammation, hypercoagulation, and AMI on changes in echoCG parameters. Table 7 presents the results of the correlation analysis in group IA.

The role of AMI in the dilatation of the cardiac chambers in group IA was evidenced by a positive correlation between troponin I and EDVI, ESVI, and LAVI.

A close relationship between the dilatation of the cardiac cavities and inflammation was noted by a positive correlation between (1) CRP and EDVI, ESVI, and LAVI, and between (2) ferritin and EDVI and RAVI.

The pathophysiological effect of procoagulatory changes on the development of cardiomegaly was indicated by a positive correlation between the fibrinogen level and EDVI, ESVI, RAVI, and LAVI. In addition, a positive and strong correlation was detected between D-dimer and EDVI; between D-dimer and RAVI.

Microcirculation disorders, acute inflammation, and myocardial damage by COVID-19 were the main cause of the decrease in myocardial contractility. In patients with LVEF < 50% and AF, a very strong and negative correlation was noted between EF and (1) troponin I, (2) CRP and ferritin; and (3) D-dimer (Table 7).

In 20 patients with LVEF of ⩾ 50% and AF in group IB, the influence of the damaging and inflammatory effects of SARS-CoV-2 on the myocardium was noticeably weaker. Thus, a negative correlation was noted between troponin I and EF and between D-dimer and EF. A positive correlation was noted between EF and RAVI. No other statistically significant correlations were observed.

In 10 of 64 patients (15.6%) of group II (without AF) with LVEF < 50%, a moderately strong and negative correlation was detected between the CRP level and LVEF and between the D-dimer level and EF, and a significantly positive correlation was observed between the D-dimer level and RAVI.

In ⩾ 50%, blood biochemical parameters did not affect the size and the systolic function of the heart.

Thus, only patients with AF and reduced LVEF showed significant AMI and pathophysiological changes in echoCG parameters because of an inflammatory reaction and a tendency to hypercoagulability. In patients with AF and EF of ⩾ 50%, these changes were less pronounced or absent.

DISCUSSION OF RESULTS

Various mechanisms of myocardial injury in COVID-19 are described, namely, (1) direct myocardial injury, when SARS-CoV-2 uses the angiotensin-converting enzyme 2 receptor (ACE2) and CD147 to enter the cell. ACE2 is a membrane protein of the carboxypeptidase family, which is found in many human organs, including heart, kidneys, intestines, and lungs. By using spike proteins to bind to the receptor and enter the cardiomyocytes, SARS-CoV-2 initiates an inflammatory process in the myocardium. Viruses, penetrating target cells, start replication (reproduction) of their kind from the materials of the cell where they parasitize. They damage the genetic apparatus, destroy cell nuclei, and disrupt deeply the intracellular protein metabolism, and the cell may die. The products of the disturbed protein metabolism of cells serve as antigens, causing the emergence of corresponding antibodies and triggering the mechanism of autoimmune myocardial damage. Newly emerged virions invade neighboring cardiomyocytes, infecting them directly [12]; (2) development of an acute systemic inflammatory reaction and a "cytokine storm" with high levels of pro-inflammatory cytokines in the blood; (3) increased myocardial oxygen demand in acute respiratory distress syndrome (ARDS) caused by increasing hypoxia and RF; (4) ischemic damage in the presence of atherosclerotic changes in the coronary arteries and coagulopathy caused by COVID-19; (5) electrolyte imbalance, primarily hypokalemia; and (6) toxic effects of antiviral drugs on the heart [13].

Ruan et al. (2020) analyzed the case histories of 68 patients who died from COVID-19 and noted that they had high blood serum levels of troponin and myoglobin during their lifetime. The levels of troponin I, a highly specific protein released into the bloodstream from cardiomyocytes during structural damage of heart muscles, particularly during viral lesions, myocarditis, pericarditis, and HF, depend directly on the extent of myocardial damage. The authors suggested that fulminant myocarditis was the cause of lethal outcomes; however, no data from myocardial biopsy were provided [14].

In the present study, AMI in patients with AF was evidenced by high levels of troponin I, which were 9.8–12.4 times higher than in patients without AF. Moreover, in patients with AF and LVEF < 50%, the level of troponin I in the blood serum was

4.8–5.6 times higher than in patients with AF and a preserved EF, which indicated a greater amount of myocardial damage. The detected highly significant negative correlation between the level of troponin I and LVEF and the positive correlation between troponin I and indexed atrial and LV volumes in patients with EF < 50% confirmed the AMI attack in patients with AF.

According to Zylla et al. (2021), in patients with COVID-19, the risk of AF in HF is increased by 5 times. They revealed a direct correlation between the HF stage and the incidence of AF. Thus, AF was detected in 30% of cases of Grade II-III chronic heart failure (CHF) (according to the New York Heart Association) and in 30–40% of cases in patients with grade IV CHF [15].

According to our data, 27% of 74 patients with COVID-19 pneumonia and preserved LVEF were diagnosed for the first time with AF paroxysms. In 26 patients with LVEF < 50%, AF paroxysms were recorded in 61.5% of cases, which was 2.3 times more often.

Kogan et al. (2022) presented morphological and immunohistochemical evidence for myocarditis in COVID-19. A morphological study of cardiac autopsy data from 32 elderly patients revealed signs of active myocarditis. Lymphocytic infiltrates and positive PCR confirmed the viral nature of inflammation. Signs of lymphocytic pericarditis, endocarditis and pancarditis with destructive coronary disease, and thrombo-vasculitis with disseminated intravascular coagulation were observed [16]. Moreover, fatal arrhythmias may develop in patients with COVID-19, which are not associated with damage to cardiomyocytes but are caused by arrhythmogenic proinflammatory cytokines [17].

The present study revealed that high levels of inflammation markers in patients with AMI and AF, highly significant correlations between CRP, ferritin, LVEF, and increased indexed atrial, and LV volumes did not allow excluding active myocarditis. During the pandemic, conducting special examinations for diagnosing myocarditis in a large number of patients with severe and extremely severe conditions was quite difficult.

According to Coromilas et al. (2021), in the presence of COVID-19, cardiac arrhythmias occur in 12.9% of cases and 61.5% of them are AF. In such patients, LA appendage thrombus occurs more often than in patients without COVID-19 history and is characterized by parietal localization of the thrombus. This suggested that the impaired integrity and function of the endocardium, caused by its damage during acute infection, is the cause of thrombogenesis [18].

The study of the incidence and characteristics of LA appendage thrombus in 469 patients with persistent nonvalvular AF enabled Mazur et al. (2023) to conclude that parietal thrombi occur 2.5 times more often in patients after COVID-19. Logistic regression analysis showed that the probability of such thrombus formation is independently affected by previous COVID-19 and CHF [19].

According to our data, in patients with AF and LVEF < 50%, a highly significant negative correlation was found between EF and indicators of blood procoagulatory activity, namely, D-dimer, and fibrinogen. In addition, a positive correlation was noted between the levels of fibrinogen, D-dimer, and indexed atrial and LV volumes.

Bhatla et al. (2020) examined nearly 700 patients with COVID-19 and revealed a relationship between elderly age, presence of HF, and AF risk [6]. Peltzer et al. (2020), Podzolkov et al. (2022) noted that AF paroxysms during the acute course of COVID-19 occurred significantly more often in elderly patients and/or in patients with cardiovascular diseases such as AH, CHD, and CHF [20, 21].

Corradi (2006) conducted a morphological analysis of atrial myocardial regions in AF and demonstrated different degrees of their remodeling at the histological and ultrastructural levels [22]. Concomitant cardiovascular disorders contribute to this architectural disorganization of the myocardium, participating in the onset and the perpetuation of AF. The most common causes of AF are considered AH, severe LV hypertrophy, fatty and amyloid infiltration of the atrial tissue with the development of fibrosis, and LA dilatation [7, 22, 23]. Therefore, patients with new-onset AF may already have an existing substrate for the formation of this arrhythmia, and acute COVID-19 may trigger its initiation. AF recurrence in COVID-19 is registered in 23–33% of patients with ARDS and/or sepsis. In approximately 10% AF develops for the first time [24, 25].

Conclusion. In our study, the well-known thesis on the predictors of AF development (AH, CHD, LV myocardial hypertrophy, and LA dilatation) was confirmed. Besides, it was shown that having COVID-19 pneumonia, new-onset AF paroxysms were recorded in patients of middle, elderly, and late-life age with a large area of lung damage and low blood oxygen saturation. AF paroxysms occur in 27% of cases with a preserved LV EF and in 61.5% of cases with EF < 50%. Cardiomegaly is detected in 44.4% of patients with AF, and the combination of acute myocardial damage, inflammation, and high blood procoagulatory activity is important in its development mechanisms.

ADDITIONAL INFORMATION

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Review article

Features of the use of oral anticoagulants in clinical practice: focus on gastrointestinal complications

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The review article presents dates about the physiology and pathophysiology of the hemostasis system, discusses the features of the use of oral anticoagulants in clinical practice. Oral anticoagulants are drugs characterized by predictable pharmacokinetics and pharmacodynamics, a favorable efficacy and safety profile. The article considers the main clinical and pharmacological characteristics of apixaban, rivaroxaban and dabigatran (bioavailability, metabolism, excretion); factors that increase the risk of gastrointestinal bleeding associated with anticoagulant therapy; drug interactions; the possibility of gastroprotection in patients taking oral anticoagulants. In real clinical practice, the reason for not prescribing or unreasonably reducing the dose of oral anticoagulants is the fear of bleeding. In this case, the risks of bleeding, as a rule, are overestimated. Knowledge of bleeding risk factors, prognostic scales and management of risk factors is an approach that can improve the safety of anticoagulant therapy. In clinical practice, the choice of the ideal oral anticoagulants, in addition to taking into account the risk of bleeding, should be based on a comprehensive assessment, including an assessment of the patient's age, risk of stroke and coronary events, renal function, and predicted compliance.

Keywords: apixaban; rivaroxaban; dabigatran; pharmacokinetics; bioavailability; adverse drug reactions; gastrointestinal bleeding.

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Обзорная статья

Особенности применения пероральных антикоагулянтов в клинической практике: фокус на желудочно-кишечные осложнения

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В обзорной статье представлены данные о физиологии и патофизиологии системы гемостаза, обсуждаются особенности применения прямых пероральных антикоагулянтов (ПОАК) в клинической практике. ПОАК – препараты, характеризующиеся прогнозируемой фармакокинетикой и фармакодинамикой, благоприятным профилем эффективности и безопасности. В статье рассмотрены основные клинико-фармакологические характеристики апиксабана, ривароксабана и дабигатрана (биодоступность, метаболизм, выведение); факторы, повышающие риск желудочно-кишечных кровотечений, ассоциированных с антикоагулянтной терапией; межлекарственные взаимодействия; возможности гастропротекции у пациентов, принимающих ПОАК. В реальной клинической практике причиной не назначения или необоснованного снижения дозы ПОАК является опасение кровотечений. При этом риски кровотечений, как правило, переоцениваются. Знание факторов риска кровотечений, прогностических шкал и управление факторами риска – подход, способный повысить безопасность антикоагулянтной терапии. В клинической практике выбор идеального ПОАК, кроме учета риска кровотечений, должен базироваться на комплексной оценке, включая возраст пациента, риск инсульта и коронарных событий, функцию почек, а также прогнозируемую комплаентность.

Ключевые слова: апиксабан; ривароксабан; дабигатран; фармакокинетика; биодоступность; нежелательные лекарственные реакции; желудочно-кишечные кровотечения.

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BACKGROUND

The hemostasis system is a complex biological system of adaptive reactions aimed at maintaining the liquid state of circulating blood, arrest of bleeding in the case of vessel damage, and lysing blood clots that have fulfilled their function. Hemostasis is implemented to balance the interaction between coagulation and anticoagulation systems. The coagulation system includes a vascular platelet and coagulation aspect, whereas the while anticoagulation system consists of natural anticoagulants and a fibrinolysis system that lyses blood clots [1, 2]. Under physiological conditions, a thrombus occurs at the site of vascular wall damage to stop bleeding and minimize the occurrence of massive blood loss. A thrombus represents a lifetime blood clot in a vessel lumen, which is a result of coagulation system activation [2].

Rudolf Virchow, a German scientist, conducted a series of studies in the mid-to-late XIX century and identified the main predisposing factors for thrombogenesis. According to the "Virchow triad", a blood clot is formed for three main reasons, namely, blood flow impairment (slowdown and turbulence), vessel wall damage, including endothelium pathology, and change in the blood component [3].

In the early stages of anthropogenesis, bleeding risks in placental mammals and anthropoid apes were extremely high. Evolutionary changes in the environment when anthroposociogenesis contributed to a decrease in the probability of traumatic injuries and bleeding in the presence of multiple risk factors for pathological thrombosis. Physical inactivity, eating disorders, and excessive accumulation of adipose tissue can cause the development of several diseases of the endocrine and cardiovascular systems, which increase thrombosis risk. Endothelial dysfunction and atherosclerotic plaques predispose individuals to arterial thrombosis formation. Insufficient physical activity and venous bed pathology increase the risk of deep vein thrombosis (DVT) of the lower extremities and thromboembolic complications. Diseases of civilization (obesity, arterial hypertension, dyslipidemia, and type 2 diabetes mellitus) are significant risk factors for both arterial and venous thromboses [4–7].

In the 21st century, diseases with a significant or main role of thrombogenesis in pathogenesis are a key medical problem. Myocardial infarctions and ischemic strokes are topical examples of arterial thrombosis. Lower-limb DVT, including those complicated by pulmonary artery thromboembolia (PATE), are common variants of venous thrombosis. In patients with atrial fibrillation (AF), the left atrial appendage is a common site for thrombus formation. From this area, a thrombus can migrate into the aorta and enter the internal carotid artery, causing acute ischemic cerebrovascular accident (ACVA) [3, 8].

Observational case-control cohort studies have contributed to the identification of risk factors for thrombosis, thromboembolic complications, and creation of scales that predict the risks of thrombotic complications, such as the Caprini scale (risk of thrombotic complications in patients undergoing surgery), CHA2DS2VASc scale (risk of thrombotic complications in patients with AF), Geneva index (risk of PATE), and Wells scale (risk of PATE). Physicians used these scales to assess the risk of thrombotic complications and the need for antithrombotic prevention [9–11]. Antiplatelet agents, anticoagulants, and fibrinolytic agents are drugs used in clinical practice for the treatment of thrombosis and thromboembolic complications. Antiplatelet agents are key drugs for the prevention and treatment of arterial thrombosis, myocardial infarction, and ACVA. Anticoagulants are used to prevent and treat arterial and venous thromboses [12]. A special group is represented by patients with ischemic ACVA who have the highest risk of thromboembolic complications. According to Diener's law, after exclusion on the day of a hemorrhagic stroke, the anticoagulant therapy is resumed according to the principle of 1:3:6:12. It is performed on day 1 in patients with a transient ischemic attack, day 3 with a minor stroke, day 6 with a moderate stroke, and day 12 with a severe stroke [13]. Patients with ACVA often have not only chronic diseases of the gastrointestinal tract (GIT) but also stress-dependent lesions of the gastroduodenal mucosa (Cushing's ulcer). The peculiarity of the management of these patients is the lack of practice of routine endoscopic examination of the upper GIT and the combined use of anticoagulants with proton pump inhibitors (PPIs), including parenteral forms [14–16].

Currently, direct oral anticoagulants (DOACs) are the main anticoagulant drugs used for prophylaxis in outpatients. These drugs are characterized by predictable pharmacokinetics and pharmacodynamics and a favorable efficacy and safety profile. Unlike heparin and low-molecular-weight heparins, DOACs have an oral route of administration and are not inferior in efficiency, and some of them are superior to the vitamin K antagonist warfarin [17].

In the Russian Federation, three drugs belonging to the DOAC class are registered, namely, dabigatran, a reversible competitive direct inhibitor of thrombin, and rivaroxaban and apixaban which are reversible, highly selective direct inhibitors of factor Xa [18–21].

In actual clinical practice, the fear of bleeding is a reason for not prescribing or unreasonably reducing the dose of DOACs. Moreover, bleeding risks are usually overestimated [22]. In AF, the HAS-BLED scale is recommended to assess the risk of hemorrhage during DOAC therapy [23]. According to current clinical guidelines, a high bleeding risk should not be a reason to refuse anticoagulant therapy because the benefits of treatment (reducing the risk of thrombosis) outweigh significantly bleeding risks in various locations [20].

The awareness of bleeding risk factors, prognostic scales, and management of risk factors can improve the safety of anticoagulant therapy. In clinical practice, the choice of the ideal DOAC, in addition to considering the bleeding risk,

should be based on a comprehensive assessment, including an assessment of the patient's age, stroke risk, coronary events, renal function, and predicted compliance.

Pharmacokinetics of direct oral anticoagulants

To date, a series of randomized double-blind international studies have demonstrated the efficiency of DOACs in preventing stroke and systemic embolic events in patients with non-valvular AF [24–27].

Literature data demonstrate that DOACs have predictable pharmacokinetics, fewer drug interactions, and better efficacy and safety profile than warfarin. The two classes of DOACs, direct thrombin inhibitors and direct factor Xa inhibitors, are fixed-dose targeted drugs, do not require international normalized ratio monitoring, and are characterized by a broad therapeutic index, rapid onset of action, and short half-life [27]. The standard doses of DOACs (dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, and apixaban 5 mg twice daily) have been reported in patients with AF [17]. In some clinical situations, for example, in renal failure, drug doses may be revised in accordance with current instructions.

The safety of the use of these drugs in specific clinical situations and the prediction of risk of adverse drug reactions (ADRs), which are mainly dose-dependent and predictable, remains unestablished [28]. Moreover, the pharmacokinetic parameters of the main representatives of DOACs and their safety profiles differ significantly. These pharmacokinetic characteristics are presented in Table 1 [19–21].

Dabigatran is a prodrug metabolized by esterase enzymes. Genetic polymorphism of esterases can cause significant differences in drug metabolism and pharmacokinetics, acting as a factor that determines the risk of side effects, particularly bleeding [29]. Dabigatran has a high polarity that prevents absorption in the GIT. Food intake slows down significantly drug absorption but does not change bioavailability (6.5%). Considering low bioavailability, creation of high concentrations in the intestinal lumen, and partial activation of the drug by intestinal esterase, dabigatran etexilate can locally affect the intestinal mucosa, causing damage and bleeding, including from existing defects [30, 31]. After the oral administration, the drug reaches maximum concentrations in the blood after 0.5–2 h, and 85% is excreted by the kidneys; therefore, a creatinine clearance of < 30 mL/min is a contraindication to the prescription of dabigatran. To reduce the risk of ADR in patients aged > 80 years, patients with erosive esophagitis and gastritis, and other patients with a high bleeding risk, a reduced dose of dabigatran is recommended (110 mg two times a day). Given that the prodrug of dabigatran etexilate is a P-glycoprotein (P-gp) substrate, co-administration of dabigatran with inhibitors and inducers of the P-gp transporter has been studied. The simultaneous use of P-gp inhibitors (amiodarone, verapamil, quinidine, ketoconazole for systemic use, dronedarone, ticagrelor, and clarithromycin) led to an increase in the plasma concentrations of dabigatran. In a non-interventional prospective study of patients aged > 85 years, the bleeding risk increased approximately sixfold when dabigatran was co-administered with the potent P-gp inhibitor amiodarone [32]. In accordance with the instructions, the simultaneous use of dabigatran with ketoconazole, cyclosporine, itraconazole, tacrolimus, and dronedarone is contraindicated, and they must be cautiously used together with amiodarone, verapamil, quinidine, and ticagrelor. When combined with verapamil, the dose of dabigatran should be reduced to 110 mg twice daily [20].

Rivaroxaban is rapidly absorbed and reaches peak plasma concentrations within 2–4 h. Food intake increases bioavailability up to 100%, probably due to the solubilization and dissolution of the drug. Rivaroxaban is a substrate for P-gp and is metabolized in the liver, with the participation of the cytochrome P450 system (CYP3A4 and CYP2J2) [33].

Table 1. Main pharmacokinetic parameters of direct oral anticoagulants

Indicator	Rivaroxaban	Apixaban	Dabigatran
Mechanism of action – point of application	Xa inhibitor	Xa inhibitor	IIa inhibitor
Bioavailability, %	66–100*	~50	6.5
Prodrug	no	no	yes
T1/2, hours	5–13	12	12–14
T max, hours	2–4	3–4	0.5–2
Plasma protein binding, %	>90	87	35
Renal excretion, %	33	27	85
Hepatic metabolism	Moderate	Moderate	Low
Metabolism in CYP450	CYP3A4, CYP2J2	CYP3A4/5	No
Drug interactions	CYP3A4 inhibitors, P-glycoprotein	CYP3A4 inhibitors	Rifampicin, quinidine, amiodarone, P-glycoprotein inhibitors
Dosing regimen	Once daily	Twice a day	Twice a day

* The bioavailability of rivaroxaban is dose-dependent: for 10 mg, approximately 100% regardless of food intake; for 15 mg and 20 mg, approximately 66% when taken on an empty stomach and approximately 100% when taken with food.

The drug has a double route of excretion, which provides greater safety in patients with hepatic and/or renal insufficiency. Considering the direct excretion of nearly a third of the drug in the urine, creatinine clearance of 30–49 mL/min is an indication for prescribing a reduced dose of 15 mg once a day. The drug is contraindicated in patients with creatinine clearance of < 15 mL/min [19].

Apixaban is absorbed mainly in the small intestine, with a drug bioavailability of 50% [34]. Apixaban is metabolized by CYP3A4/5 and secondarily by sulfotransferase 1A1 and excreted in the urine (25%) and hepatobiliary route (75%). The drug should be used with caution in patients with severe renal insufficiency, and it is contraindicated in patients with a creatinine clearance of < 15 mL/min. A reduced dose of 2.5 mg twice daily is indicated if two or more of the factors are present: age ⩾ 80 years, body weight < 60 kg, and plasma creatinine of ⩾ 1.5 mg/dL (133 μmol/L). In addition, a dose of 2.5 mg twice a day is prescribed for patients with creatinine clearance of 15–29 mL/min [21]. A retrospective study by Hanigan et al. published in 2020 revealed that the co-administration of moderate CYP3A4 inhibitors (amiodarone, diltiazem, verapamil, erythromycin, etc.) with apixaban or rivaroxaban for at least 3 months was associated with a higher overall bleeding risk compared with DOAC monotherapy [35]. Clinically significant drug interactions of major DOACs are presented in Table 2.

All DOACs are contraindicated in patients with liver diseases accompanied by coagulopathy, significant bleeding risk, and Child–Pugh class C liver function impairment [19–21]. According to the European Heart Rhythm Association (EHRA) of 2021, rivaroxaban is contraindicated in patients with Child–Pugh grade B hepatic cirrhosis, whereas other DOACs can be used with caution. In the latest updates of the 2021 EHRA European Clinical Guidelines, unreasonable frequent prescriptions of reduced doses of DOACs received much interest. Experts emphasize the need for routine use of the studied standard doses of anticoagulants and reduced doses only in accordance with published and approved criteria. When choosing a dose, the interests of the patient, whose stroke risk prevails over the risk of hemorrhagic complications, must be considered [36]. Russian researchers take a similar position, pointing to an unreasonably frequent reduction in DOAC doses [37].

Effect of direct oral anticoagulants on the gastrointestinal mucosa

Despite the relatively favorable safety profile of DOACs, bleeding risk, including GI bleeding, is predominant and determines the choice of DOACs. Currently, no studies have directly compared the safety and efficacy of various DOACs. Randomized clinical trials have shown that the incidence of various hemorrhagic complications during anticoagulant therapy is 2–5% annually [38, 40]; however, when analyzing registries of patients with AF receiving long-term DOAC therapy, the frequency of major bleeding was approximately 0.5% [41, 42]. GI bleeding account for at least half of the total cases of major bleeding [43–45]. In a long-term prospective study within the REVAZA registry, the incidence of bleeding from the upper GIT was registered three times more often than that from the lower GIT [45].

Considering pharmacokinetics and pharmacodynamics, DOACs should not have a direct damaging effect on the GI mucosa. Mihalkanin et al. demonstrated that within 3 months of monitoring patients who initially had no lesions in the gastric mucosa and received DOACs, no clinically significant GI hemorrhage (GIH) was detected [46]. A high

Table 2. Clinically significant drug interactions between direct oral anticoagulants and commonly used drugs [19–21]

Agent	Apixaban	Dabigatran	Rivaroxaban
Antibacterial drugs			
Clarithromycin	No	No	No
Erythromycin	No	No	No
NSAIDs and antiplatelet agents			
NSAIDs	*	*	*
Aspirin	*	*	*
Clopidogrel	Yes	*	No
Ticagrelor	No	*	No
Antiarrhythmic drugs			
Amiodarone	Yes	*	No
Quinidine	Yes	Yes	No
Verapamil	No	*	No
Diltiazem	No	No	No

Note. Yes, there is an interaction (it is not advisable to prescribe); no, no clinically significant interaction (preferably prescribed); * with caution (subject to the measures specified in the instructions, taking into account possible changes in the concentration).

bleeding risk is associated with the "manifesting effect" of drugs on existing mucosal defects [47]. Thus, in a meta-analysis of 43 studies involving > 160,000 patients treated with DOACs, the incidence of GIH from the upper regions was 1.5% annually and 1.0% from the lower ones, which were mainly caused by tumors of various localization, diverticulitis, colon polyps, ulcerative colitis, hemorrhoids, and rectal fissures [48].

Thus, DOACs have a "manifesting" effect on the already altered GI mucosa, and bleeding risk during anticoagulant therapy depends on the profile of a patient and risk predictors. Epidemiological studies have shown that GIH risks are significantly increased in patients with comorbidities. The main predictors of bleeding were *Helicobacter pylori* infection with an odds ratio (OR) of 4.75; age > 75 years, OR of 4.52; alcohol addiction, OR of 2.5; renal failure, OR of 1.67; coronary heart disease, OR of 1.37; chronic heart failure, OR of 1.25; and glucocorticosteroid intake, OR of 1.17 [49, 50].

Before prescribing DOACs, in terms of preventing the risk of complications, erosive and ulcerative damage to the mucous membrane, *H. pylori* infection, oncopathology, diverticulitis, and other clinically important diseases of the GIT, which are potential sources of bleeding, must be ruled out. In this regard, prompt endoscopic examination of the upper and lower GIT is required [51]. To determine the approach of managing a patient receiving anticoagulant therapy, with GI bleeding, the classification of hemorrhagic complications based on the GARFIELD-AF registry (Table 3) is used [37].

Minor hemorrhagic bleeding or "vexatious" hemorrhage does not require medical intervention, changes in the treatment regimen, does not change the patient's habitual activity, and includes minor hemorrhoidal bleeding, minor nosebleeds, subcutaneous hematomas, and gingival bleeding. According to the ORBIT-AF registry, which included 7372 patients on DOAC therapy, 20% experienced "vexatious" bleeding, whereas 96% continued anticoagulant therapy without changes. Over the next 6 months, when comparing patients with "vexatious" bleeding and those without it, the risk of major hemorrhagic complications was not different. Thus, minor hemorrhagic complications are not prodromes of major bleeding, do not pose a serious threat to health, do not affect the long-term prognosis of patients, and do not serve as an indication for the discontinuation of therapy [52]. Kirchhof et al. demonstrated that when anticoagulant therapy is interrupted, the risk of stroke increases, namely, by 6.2% with temporary discontinuation and by 25.6% with long-term cancelation [53]. According to the Russian clinical guidelines of 2020, to prevent thromboembolic complications in patients with AF and minor "vexatious" bleeding, postponing the intake of one dose of DOAC until the bleeding stops is sufficient [51].

Currently, the scientific literature presents heterogeneous data on the comparative safety of the main DOACs in terms of the development of GIT complications, which is associated with different study designs.

According to the Italian National Pharmacovigilance Network, 7273 serious ADRs were registered in 959.231 patients treated with DOACs — 3342/294721 (1.13%) for dabigatran, 2032/317359 (0.64%) for rivaroxaban, and 1492/294721 (0.50%) for apixaban. The most frequent severe ADRs were GI bleeding (41.2% of cases) [54].

In a national population study, Ingason et al. analyzed the data of 8892 patients who received therapy with various DOACs between 2014 and 2019 (Table 4) [55].

Ingason et al. revealed that rivaroxaban therapy was associated with an increased overall risk of GIH and risk of major GIH compared with apixaban and dabigatran. The causes of the increased risk in patients taking rivaroxaban are unclear; however, the findings may be related to the study design.

Higher bleeding rates with rivaroxaban intake should be further analyzed. A randomized controlled trial of the efficacy and safety of rivaroxaban (ROCKET AF) involved more patients with severe diseases who initially had high bleeding risk [56].

GIH prevention

DOACs are used to prevent and treat potentially life-threatening conditions (thrombosis and PATE); however, their uses are at risk of ADRs, particularly bleeding. In clinical

Table 3. Classification of hemorrhagic complications based on the GARFIELD-AF registry

Major hemorrhagic complications	Overt bleeding with at least one of the following: • Decrease in hemoglobin by ≥2 g/dL or • Need for blood transfusion ≥2 doses of blood components • Clinically significant localization (intracranial, intraspinal, intraocular, cardiac tamponade, intra-articular, intramuscular with the development of compression syndrome, and retroperitoneal bleeding) • Fatal bleeding
Minor clinically significant hemorrhagic complications	Overt bleeding that did not meet the criteria for major hemorrhage but required medical treatment, a change in the treatment regimen by the doctor, or accompanied by pain, discomfort, or a change in the patient's usual activity
Minor hemorrhagic complications	All other bleeding events that do not meet the criteria for major and minor clinically significant hemorrhage

Table 4. Incidence of gastrointestinal (GI) hemorrhage (GIH) according to a population study (*n* = 8892)

Therapy DOACs	Events per 100 people/years
Total of GI hemorrhage	
Apixaban	2.4
Dabigatran	1.6
Rivaroxaban	3.2
Major GI hemorrhage	
Apixaban	1.4
Dabigatran	1.1
Rivaroxaban	2.0
Bleeding from the upper GI tract	
Apixaban	0.8
Dabigatran	0.4
Rivaroxaban	1.0
Bleeding from the lower GI tract	
Apixaban	1.3
Dabigatran	1.2
Rivaroxaban	1.6

practice, to assess the risk of all hemorrhagic complications when using DOACs, the HAS-BLED scale is recommended. Patients who scored ⩾ 3 points on this scale have a high bleeding risk [57]. According to the algorithm of the Eurasian Association of Therapists for the Prevention of Hemorrhagic Complications, patients with AF receiving DOACs should have normal blood pressure, minimized risk of drug interactions, and refused or minimized alcohol consumption, and the efficiency and safety of anticoagulant therapy must be evaluated at least once every 12 months, as well as liver and kidney function. Patients aged > 75 years should be followed up every 6 months, and those with creatinine clearance < 60 mL/min once every N months (N = creatinine clearance /10) [21, 58].

Before initiating DOAC therapy, erosive and ulcerative lesions of the GI mucosa must be ruled out. Patients with high bleeding risk require correction of modifiable risk factors, such as eradication of *H. pylori*, minimizing or canceling glucocorticosteroids and NSAIDs, and use safer NSAIDs and antiplatelet agents (highly selective cyclooxygenase-2 inhibitors and adenosine diphosphate receptor blockers), and acid-suppressive and gastroprotective therapy [51].

The COMPASS study was the first clinical randomized trial to evaluate the efficacy and safety of PPIs in patients receiving DOACs. That study revealed that PPIs did not affect the GIH risk when using DOACs; however, they had a positive effect on patients from the high-risk group [59]. Thus, PPIs are recommended for all patients who scored ⩾ 3 on the HAS-BLED scale [63]. PPIs should also be given to patients receiving dual or triple antithrombotic therapy, patients taking a combination of DOACs with NSAIDs and/or glucocorticosteroids, and patients with concomitant acid-related diseases [60].

In some clinical situations (hypo- or anacidity, duodenogastric reflux, microcirculation disorders, and use of NSAIDs and other drugs that affect adversely the GI mucosa), antacids, alginates, rebamipide, bismuth tripotassium dicitrate, and ursodeoxycholic acid can be used. No clinical studies have evaluated the efficiency of these drugs in patients receiving anticoagulants. Clinical studies have demonstrated the effectiveness of rebamipide in patients with NSAID gastroenteropathy by increasing the concentration of prostaglandins in the GI mucosa, increasing the synthesis of glycoproteins, and activating epidermal growth factor and its receptor expression [61–64].

CONCLUSIONS

Currently, DOACs have a wide range of clinical indications, including the prevention and treatment of thrombotic and thromboembolic complications. Hemorrhagic complications, particularly from the GI tract, is the most common ADRs associated with DOAC therapy. When deciding on DOAC therapy, in each case, bleeding risk, age, risk of stroke or coronary events, renal function, and predicted adherence to the therapy prescribed must be considered. To minimize GIH risk, risk factors for bleeding must be identified, modifiable factors altered, potential drug interactions monitored, and, if necessary, acid-suppressive and gastroprotective therapy prescribed.

ADDITIONAL INFORMATION

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Review Article

Atrial fibrillation in patients with chronic kidney disease: features of pathogenesis and treatment

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Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia in adults, the frequency of which increases in patients with chronic kidney disease (CKD). The substrate for the development of AF is atrial cardiomyopathy, which includes structural, electrophysiological and molecular remodeling of the atria. AF, in turn, can initiate and accelerate the progression of CKD. Such a bidirectional relationship causes a frequent combination of these two conditions, leading to both a prothrombotic state and an increased risk of bleeding. In patients with CKD, the pharmacokinetics of drugs used in AF are changing, what limits their use in CKD S4/S5. If previously patients with CKD S4-5 were excluded from randomized clinical trials (RCTs) on treatment strategies for AF, a number of such studies on their management have been published to date. The purpose of the article is to review existing ideas about the features of the pathogenesis of AF in CKD and strategies of recent years for the treatment of AF with advanced stages of CKD.

Keywords: chronic kidney disease (CKD); atrial fibrillation (AF); pathophysiology; inflammasoma; atrial fibrosis; treatment.

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Обзорная статья

Фибрилляция предсердий у пациентов с хронической болезнью почек: особенности патогенеза и лечения

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Фибрилляция предсердий (ФП) наиболее часто диагностируемая сердечная аритмия у взрослых, частота которой увеличивается при хронической болезни почек (ХБП). Субстратом развития ФП является предсердная кардиомиопатия, включающая в себя структурное, электрофизиологическое и молекулярное ремоделирование предсердий. ФП, в свою очередь, может инициировать и ускорять прогрессирование ХБП. Такая двунаправленная взаимосвязь обусловливает частое сочетание этих двух состояний, приводящее как к протромботическому состоянию, так и к повышению риска развития кровотечений. У пациентов с ХБП меняется фармакокинетика лекарственных препаратов, используемых при ФП, что ограничивает их применение при ХБП 4-5-й стадии. Ранее пациентов с ХБП 4-5-й стадии исключали из рандомизированных клинических исследований (РКИ) по лечебным стратегиям при ФП, однако к настоящему времени опубликован ряд исследований по их лечению. Цель статьи — обзор существующих представлений об особенностях патогенеза ФП при ХБП и стратегий последних лет по лечению ФП с поздними стадиями ХБП.

Ключевые слова: хроническая болезнь почек (ХБП); фибрилляция предсердий (ФП); патофизиология; инфламмасома; предсердный фиброз; лечение.

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ЭКО•ВЕКТОР

BACKGROUND

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia in adults around the world, the global prevalence of which tends to increase [1]. AF is associated with serious complications such as stroke and heart failure leading to significant morbidity and mortality [2, 3]. Chronic kidney disease (CKD) is one of the risk factors for the development of AF, defined as the presence of markers of kidney damage (albumin/creatinine ratio > 30 mg/g in a single urinalysis is usually used for screening) or a decrease in glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2, persisting ⩾ 3 months. Based on the presence of markers of damage and the level of GFR, the following stages of CKD are distinguished: S1 — ⩾ 90 (high or optimal), S2 — 60-89 (slightly reduced), S3a — 45–59 (moderately reduced), S3b — 30–44 (significantly reduced), S4 — 15–29 (drastically reduced), S5 — < 15 ml / min / 1.73 m^2 (end-stage renal disease, ESRD) [4]. CKD is a rapidly growing public health problem, with a global prevalence of CKD estimated at 9.1–13.4% [4, 5]. Patients with CKD demonstrate an increased risk of developing AF and other cardiovascular diseases, which are the most common cause of death in CKD patients [4].

CKD and AF have a number of common predisposing factors, including arterial hypertension, coronary heart disease, and diabetes mellitus [6–8]. Patients with CKD are characterized by such comorbidity, however, even after adjustments for many co-factors, CKD remains an independent factor in the development of AF [6, 8]. In turn, AF can initiate and accelerate the progression of CKD. Such a bidirectional relationship causes a frequent combination of these two conditions, which worsens the prognosis, leads, on the one hand, to a prothrombotic state, and, on the other hand, to an increased risk of bleeding. Renal dysfunction is accompanied by a change in the pharmacokinetics of many drugs that are indicated for use in people with CKD, including direct oral anticoagulants (DOACs), which limits their use in S4-5 CKD. However, since the risk of thromboembolic complications increases with decreasing GFR, more so than the risk of bleeding, efforts continue to find the optimal treatment for AF in this patient population. While previously patients with AF and S4-5 CKD were excluded from randomized clinical trials (RCTs) on treatment strategies for AF, a number of RCTs on the tactics of managing these patients have been published to date [9–11].

EPIDEMIOLOGY

A meta-analysis of the risk of developing AF depending on kidney function in a study that included 16.769 participants of different ethnic groups, divided by categories of decrease in estimated GFR (eGFR), showed a gradual increase in the risk of developing AF: RR (95% CI) was 1.00, 1.09 (0.97–1.24), 1.17 (1.00–1.38), 1.59 (1.28–1.98) and 2.03 (1.40–2.96) at S1, S2, S3a, S3b, S4, respectively [12]. A South Korean study (*n* = 4,827,987) also noted an increase in the risk of developing AF depending on the severity of CKD: RR (95% CI) was 1.77 (1.69–1.85), 1.85 (1.85 80–1.91), 1.99 (1.95–2.04) and 4.04 (3.07–5.33) in persons with CKD stages 1, 2, 3 and 4, respectively, compared with persons without CKD [13]. In the ARIC study (*n* = 10328), a decrease in eGFR to 30–50 and 15–29 ml/min/1.73 m^2 was accompanied by an increase in the risk of developing AF by 1.6 and 3.2 times compared with that in individuals with normal renal function [14]. In a meta-analysis of 25 RCTs of patients with ESRD, the incidence of AF was 11.6% of patients [15]. In general, it is believed that the prevalence of AF in CKD is 2–3 times higher than AF in the general population [7]. And, conversely, as the analysis of the Russian REQUAZA registry showed, almost half of patients with AF may have concomitant renal pathology [16].

POTENTIAL MECHANISMS FOR THE DEVELOPMNT OF ATRIAL FIBRILLATION IN CHRONIC KIDNEY DISEASE

The mechanisms of development of AF are not fully understood. The substrate for AF is atrial cardiomyopathy, which is a complex of structural, electrophysiological, and molecular changes in the atrial myocardium that can cause and maintain AF [2]. The term "atrial cardiomyopathy" and the definition were given by the experts of the international Working Group formed by the European Heart Rhythm Association (EHRA), the International and Asia-Pacific Heart Rhythm Societies (HRS and APHRS respectively) and the Latin American Society for Cardiac Pacing and Electrophysiology (SOLAECE). The consensus report published by EHRA/HRS/APHRS/SOLAECE presents a classification of atrial cardiomyopathy and summarizes the existing concepts of structural and electrophysiological remodeling of the heart in AF [17].

As already noted, the development of AF in CKD has a number of common risk factors with other diseases, however, non-traditional risk factors for the development of AF are identified. These include activation of the renin-angiotensin-aldosterone system (RAAS) and hyperactivity of the sympathoadrenal system (SAS), oxidative stress, systemic inflammation, electrolyte disturbances, accumulation of uremic toxins, and chronic anemia [6–8]. These factors are difficult to isolate from others involved in atrial remodeling and are common risk factors for the development of AF, leading to atrial volume or pressure overload, however, the contribution of “renal” factors to the development of AF is generally recognized [6, 8]. Traditional Framingham risk factors for cardiovascular disease have a weak predictive power in CKD, and the addition of specific renal factors significantly improves the correlation [18].

Renin-angiotensin-aldosterone system (RAAS). Activation of the RAAS and its mediators is a major factor in the pathogenesis and progression of CKD [7].

Angiotensin II (AngII) has profibrotic activity. AII in combination with aldosterone promotes the production of reactive oxygen species by activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which in turn stimulates the production of transforming growth factor β1 (TGF-β1). In general, the RAAS, with the help of its mediators, initiates oxidative stress and the synthesis of profibrotic growth factors, the production of pro-inflammatory cytokines, cell adhesion molecules, extracellular matrix proteins, plasminogen activator inhibitor-1 (PAI-1), promotes the activation of macrophages [7]. RAAS activation is seen as an important link between CKD and AF. In the formation of an arrhythmogenic substrate in the heart in AF, three interrelated pathways are believed to be involved — RAAS, TGF-β1 and oxidative stress; the atria appear to be more susceptible to fibrosis than the ventricles [7, 19]. In a transgenic mouse model overexpressing the constitutively active form of TGF-β1, selective atrial fibrosis was observed, which led to heterogeneous conduction and increased atrial vulnerability to AF [20]. RAAS can also induce the activation of the TGF-β1/Smad2/3 pathway, which is also promoted by an increased level of reactive oxygen species and oxidative stress [21]. An experimental decrease in TGF-β1 expression with pirfenidone reduces the degree of fibrosis in the lungs, liver, kidneys, and heart [7]. A study in nephrectomy rats, which are used to model the pathogenesis of human CKD, demonstrates the role of oxidative stress mediated by NADPH oxidases in causing left atrial fibrosis and increased vulnerability to AF. Treatment with a powerful antioxidant, zinc sodium dihydrolipoyl histidinate, was effective in reducing the inducibility of AF [7, 22].

Inflammation. CKD is considered a systemic inflammatory disease with many causes [23]. Elevated levels of inflammatory markers (IL-6, tumor necrosis factor-α, C-reactive protein, etc.) are found in the early stages of CKD, which become more significant as the disease progresses [24]. It is also known that elevated blood levels of pro-inflammatory cytokines and inflammatory markers are associated with an increase in the frequency and persistence of AF [25]. There is no evidence of a direct relationship between the level of circulating inflammation markers and the formation of fibrosis in the atria, however, data have been obtained on the activation of the NLRP3 inflammosome in cardiomyocytes in AF and its role in atrial remodeling in CKD [21, 26]. Compared to the well-established canonical function of the NLRP3 inflammasome in innate immune cells, mediating caspase-1 activation and interleukin-1β (IL-1β) release, the role of the NLRP3 inflammasome in cardiac cells and other non-immune human cells is less well known. The first study that provided evidence of NLRP3 inflammasome activation in heart cells as a key event in the pathogenesis of AF was published in 2018 [26]. Cardiomyocyte-specific knockdown in a mouse model (CM-KI) expressing constitutively active NLRP3 inflammasomes only in cardiomyocytes caused 100% premature atrial contractions with a significant increase in induced AF. MCC950, a selective inflammasome inhibitor, successfully reduced induced AF in CM-KI mice [26].

In the same year, the results of a study were presented demonstrating the presence in the atrial myocardium of rats serving as a model of CKD, components of the NLRP3 inflammasome activation and other biological pathways (Fig. 1) involved in the formation of an arrhythmogenic substrate in CKD [21]. The CKD model in the study was rats, in which 3 months after partial nephrectomy (of the right kidney and nephrotomy 5/6 of the left kidney), the level of circulating creatinine and urea was significantly increased. Also, at that time there were signs of RAAS activation: the blood level of AngII and TGFβ1 was 3 times higher than in the control, which was served by rats without CKD after laparotomy without kidney resection. The left atrial tissue (LA) was quantitatively tested for the severity of fibrosis and inflammation, expression of type I collagen, α-SMA (α-smooth muscle actin), CTGF (connective tissue growth factor), N-cadherin, expression and distribution of connexins 40 and 43 (Cx40 and Cx43 are the two major functional subunits of intercellular gap junctions in the atria) using immunohistochemistry. Any changes in expression, phosphorylation (regulator of gap channel activity in the transport of molecules, Ca ions) and distribution of atrial connexins were considered as proarrhythmic. The amount of TGFβ1, phosphorylated (activated) Smad 2 and Smad 3 (signal transduction mediators), α-SMA, type I collagen, NLRP3, ASC (inflammasome component), caspase-1, IL-1β, IL-18, Rac-1, Cx40, Cx43 (total and phosphorylated) were assessed in the atria by Western blotting. According to echocardiography, uremia in rats led to an increase in LA and left ventricular hypertrophy (LVH) without functional changes in the latter. There was a significantly higher frequency of AF occurrence provoked by atrial electrical stimulation in the CKD group compared with the control group ($p < 0.001$) and the duration of AF paroxysms in CKD ($p < 0.001$). Studies using immunohistochemistry, biochemical, enzyme-linked immunosorbent assays, and Western blotting made it possible to identify participants in the activation of biological pathways in the atrial tissue (Fig. 1). TGF-β1/Smad2/3/CTGF, NLRP3 inflammasome and connexins (Cx), present in cardiac cells, have been shown to be potential mediators of increased vulnerability to AF in CKD. Fibrosis and remodeling of Cx40/43-gap intercellular junctions are regarded as the main pathological substrate in the development of AF. There was a decrease in phosphorylated Cx43 (activated), a decrease in Cx40 and a lateral distribution (instead of diffuse) of Cx40 and Cx43 on the cell surface against the background of an increase in Rac-1 (a signaling protein from the family of small G proteins), CTGF and N-cadherin, activating the synthesis of collagen, which disrupts the function of connexins (Fig. 1) [21].

Thus, the researchers demonstrated the activation of biological pathways in the atrial myocardium, leading to

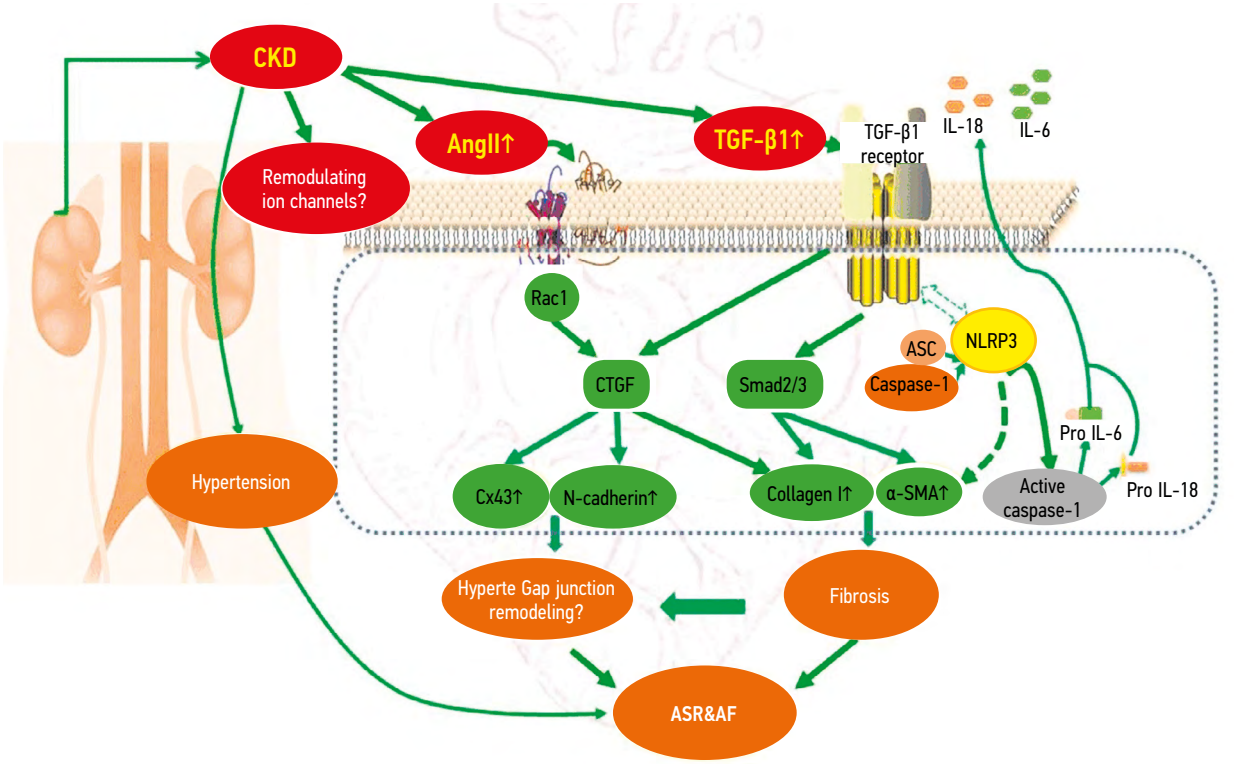

Fig. 1. Potential biological pathways involved in the formation of arrhythmogenic substrate of atrial fibrillation (AF) in chronic kidney disease (CKD). Atrial fibrosis induced by CKD may be associated with activation of the TGFβ1/Smads signaling pathway and NLRP3 inflammasome signaling pathway, and the CKD induced Cx40/43- gap junction remodeling may be connected with the Ang II-induced activation of Rac-1, CTGF and N-cadherin in atrial cells. Ang II — angiotensin II; ASC — apoptosis-associated Speck-like protein containing the C-terminal CARD domain; ASR — structural remodeling of the atria; α-SMA — α-smooth muscle actin; CTGF — connective tissue growth factor; Cx43 — connexin 43; IL-1β, -18 — interleukin-1β, -18; NLRP3 — NOD-like receptor (NLR) containing pyrin domain 3; Rac1 — intracellular protein involved in cellular signal transduction from a family of small G-proteins (small GTTases); TGF-β1 — transforming growth factor-β1 (adapted from [21])

inflammation and increased fibroplastic processes, which resulted in an extensive interstitial process in the atria and increased arrhythmogenicity, showed the relationship of these processes with azotemia, increased levels in the blood and in the atria RAAS mediators — AngII, TGF-β1 [21]. The role of RAAS in the pathogenesis of AF is supported by clinical data and studies in animal models showing that the use of angiotensin converting enzyme inhibitors reduces the incidence of AF and the level of atrial fibrosis [2, 7]. However, a complete understanding of the processes in atrial cells is still a long way off. Probably, in AF, both in the general population and in CKD, general processes in the atrial myocardium take place, and triggers may be more specific. Selective inhibition of various members of the NLRP3 inflammasome complex, the impact on participants in other biological pathways that implement the processes of atrial remodeling, may in the future become an effective therapeutic method in the prevention of AF. The large-scale clinical trial CANTOS showed that selective suppression of IL-1β with the monoclonal antibody canakinumab can significantly reduce the incidence of recurrent cardiovascular events [27].

Uremic toxins, oxidative stress, disorders of phosphorus-calcium (P-Ca) metabolism. Disruption of systemic and intracellular calcium homeostasis in CKD is a critical element in the pathogenesis of AF. Ca^{2+} plays a central role in atrial ectopic activity, re-entry formation, and electrophysiological atrial remodeling [7]. In a rat model of CKD, the effect of indoxyl sulfate (IS), a uremic toxin, on the calcium content in cardiomyocytes isolated from the left atrium (LA), right atrium (RA), sinoatrial node and orifice of the pulmonary veins (PV) was studied [28]. Important electrical changes were noted, including delayed post-depolarization in the PV, decreased spontaneous sinoatrial node activation, shortening of the LA action potential, and increased inducibility of AF. Ascorbic acid, as an antioxidant, weakened the effect of the toxin on the cardiomyocytes of LA PV, and sinoatrial node. According to the authors, the uremic toxin indoxyl sulfate promotes atrial and PV arrhythmogenesis by inducing oxidative stress and disturbances in Ca^{2+} current through ion channels, intracellular Ca^{2+} homeostasis, and may be a factor in the occurrence of AF in patients with CKD [28]. In another study, CKD led to significant disturbances in calcium homeostasis in pulmonary venous cardiomyocytes, such as an increase in the amplitude of calcium transport and calcium content in the sarcoplasmic reticulum, large sodium/calcium exchange currents, but a lower density of calcium currents in *L*-type channels due to the activation of protein kinase A and accumulation of reactive oxygen species [7]. Changes in Ca-P metabolism in CKD

predispose to valvular heart disease in the form of calcification of the mitral annulus or aortic valve, and may further contribute to the development of AF due to pressure overload. Vascular calcification, observed even in children with progressive CKD, increases afterload and is a risk factor for the development of LVH and subsequent LA overload [7].

Other uremic toxins (indole-3-acetic acid, *p*-cresol, and *p*-cresyl sulfate) that accumulate in CKD are also involved in oxidative stress, inflammation, and neurohumoral activation pathways leading to cardiovascular fibrosis and oxidative damage. The development of AF in CKD may be due to increased regulation of the SAS and an increased risk of cardiovascular diseases [7].

Molecular remodeling. In addition to the molecular processes described above that occur in atrial cardiomyopathy, new disturbances in various biological pathways in the atria are being identified. The use of next generation gene sequencing (NGS) methods allowed researchers to identify changes in 378 genes expressed in the heart in CKD [29]. Quantitative analysis of the expression of RNA transcripts showed genes with significantly increased expression, among which were the genes for stress-induced proteins — CIRP (cold-induced RNA-binding protein) and RBM3 (RNA-binding motif protein), associated with the functioning of ion channels, and changes in their expression may underlie ion channel remodeling in CKD.

Studies have appeared that emphasize the role of chronic anemia and the participation of hypoxia-inducible factor 1α (HIF-1α), as well as Klotho protein (co-factor FGF23) in the development of arrhythmogenicity. The authors believe that the responses of cardiac cells to stress are potential targets for pharmacological intervention in CKD-induced cardiac arrhythmias [29].

MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE

Patient management includes stroke prevention (anticoagulation), treatment of AF in the form of symptom control (rhythm control or heart rate control), optimization of treatment of underlying and concomitant diseases.

Assessment of the risk of thromboembolic complications in patients with AF and chronic kidney disease

AF and CKD, each by itself, are risk factors for acute cerebrovascular accident (ACV). AF and CKD contribute to the formation of blood clots due to the influence on individual components of the Virchow triad [30]. In AF, ischemic stroke (IS) and systemic thromboembolism (SE) most often have a cardioembolic origin, which is associated with stagnation of blood in the LA and the formation of a thrombus in the ear, less often — in the cavity of the LA. On the other hand, endothelial dysfunction and platelet activation are noted already in the early stages of CKD, and the risk of thromboembolic complications (TEC) is increased both at the pre-dialysis stage of CKD and during dialysis [30]. The high risk of TEC is the most important problem in CKD patients with AF [6, 8]. The CHA2DS2-VASc score is recommended for stratifying the risk of stroke and systemic embolism in patients with AF in the general population and in AF with CKD. Continuous use of oral anticoagulants (OAC) with a score of ⩾ 2 in men and ⩾3 in women is associated with favorable effects in AF, including CKD (with a lower risk, the issue of prescribing OAC is decided individually) [6, 31].

Bleedings risk assessment

Patients with CKD have an increased risk of bleeding compared with the general population. Thus, the presence of reduced kidney function (GFR < 60 ml/min/1.73 m^2) leads to an increase in the risk of hemorrhagic stroke by more than 4 times in men and 7 times in women [32]. Bleeding risk scales, in particular the HAS-BLED scale, take into account the presence of CKD, and the risk of bleeding when prescribing oral anticoagulants (OAC) should be taken into account [2, 3, 6]. The value of the HAS-BLED index ⩾ 3 indicates a high risk of bleeding, but does not exclude the possibility of anticoagulant therapy, since in most cases the risk of IS and SE is higher than the risk of bleeding. Absolute contraindications to OAC therapy in CKD are the same as in the general population [6].

Prescription of OAC in CKD S1-3. VKAs (vitamin K antagonists) are effective and relatively safe in maintaining international normalized ratio (INR) in the therapeutic range > 70% of the time (TRT). The frequency of hemorrhagic and thromboembolic events correlates with the quality of VKA treatment, as assessed by TRT [2, 3, 32].

All DOACs including direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (rivaroxaban, apixaban) have a certain degree of renal excretion, ranging from 25% for apixaban to 80% for dabigatran, which should be taken into account in the treatment of patients with CKD [2, 3, 6].

The results of RCTs and observational studies have shown that in patients with mild to moderately reduced renal function — creatinine clearance (CC) 30–50 ml/min (for apixaban 25–50 ml/min), calculated according to Cockcroft-Gault, dabigatran, rivaroxaban and apixaban are equally comparable to warfarin in terms of its effect in stroke prevention [6, 32]. Also, in all major RCTs, the use of DOACs in patients with CC in the range of 30–50 ml/min (for apixaban — 25–50 ml/min) was associated with a significant reduction (~ 50%) in the risk of intracranial hemorrhage compared with warfarin [33].

In patients with moderate renal impairment, the concentration of rivaroxaban in the plasma after a dose of 15 mg once per day was identical to the concentration of rivaroxaban in the blood plasma in people with normal renal function after taking 20 mg once per day. A renal dose study was planned in the ROCKET AF design, where all patients

Table 1. Recommendations for the use of oral anticoagulant drugs in atrial fibrillation, depending on creatinine clearance[1]

CKD stage	CC, ml/min	Drug, dose, frequency
1 и 2	⩾ 90 и 60–89	Warfarin, target INR 2.0–3.0 Dabigatran[2] 150 mg twice per day or 110 mg twice per day Rivaroxaban 20 mg once per day Apixaban, 5 mg, twice per day
3	30–59	Warfarin, target INR 2.0–3.0 Dabigatran[2] 150 mg twice per day or 110 mg twice per day Rivaroxaban [3] 15 mg once per day or Rivaroxaban 20 mg once per day if CC ⩾ 50 ml/min Apixaban[4] 5 mg or 2.5 mg twice per day
4	15–29	Warfarin, target INR 2.0–3.0 Rivaroxaban [3] 15 mg once per day Apixaban [4] 2,5 mg twice per day
5	< 15 ml/min, hemodialysis	Warfarin, target INR 2.0–3.0

[1] CC — creatinine clearance estimated by Cockcroft–Gault formula;
[2] reducing the dose is not associated with CC; see Table 2 for reducing the dose criteria;
[3] reducing the dose if CC is equal to 15–49 ml/min;
[4] reducing the dose if creatinine ⩾ 133 mmol/l; for additional criteria, see Table 2.

Table 2. Recommendations for reducing the dose of oral anticoagulant drugs in atrial fibrillation [3]

	Dabigatran	Rivaroxaban	Apixaban
Standard dose	150 mg twice per day	20 mg once per day	5 twice per day
Reduced dose	110 mg twice per day	15 mg once per day	2,5 twice per day
Dose reduction criteria	• Age ⩾ 80 years • Concomitant use of verapamil or • Increased risk of bleeding	CC 15–49 ml/min[1]	At least 2 of 3 criteria: • Age ⩾ 80 years • Body weight ⩽ 60 kg or • Serum creatinine ⩾ 133 μmol/l

[1] CC — creatinine clearance estimated by Cockcroft-Gault formula

with CC 30–49 ml/min received rivaroxaban at a dose of 15 mg once per day [34]. Recommended doses of OAC are presented in Table 1.

The choice of the dose of dabigartan and apixaban in patients with CC > 30 ml / min takes into account several risk factors for bleeding indicated in the instructions (Table 2). In the absence of these recommendations for dose reduction, it is necessary to strive for the appointment of a full dose of drugs [2, 3].

Prescription of OAC in CKD S4. Given the recommendations of drug manufacturers, patients with CC < 30 ml/min have historically been excluded from RCTs on treatment strategies, so there is no evidence base for prescribing DOACs with CC ⩽ 15–29 ml/min [6]. However, according to Russian and European recommendations, the use of direct factor Xa inhibitors, apixaban and rivaroxaban (but not dabigatran) at reduced doses is allowed in patients with AF and CC 15–29 ml/min (Table 1, 2), taking into account their pharmacokinetic properties, and relying on the results obtained in 2 cohort controlled studies [2, 3, 35, 36]. At the same time, the US FDA approved the use of dabigatran at a reduced dose of 75 mg twice daily, with a CC of 15–29 ml/min [6]. VKAs have conflicting observational data on their efficacy and safety, ranging from an increased risk of death in warfarin users to a clear benefit, but their use is independent of kidney function and is not contraindicated for the prevention of stroke and SE in CKD S4-5 [6, 32].

Prescription of OAC in CKD S5 and CKD S5(D). According to the latest recommendations for AF, instructions from manufacturers of drugs registered in the Russian Federation, the use of DOACs is not indicated for patients with CC < 15 ml/min (CKD S5 and CKD S5(D)), that is, both for people without dialysis and receiving chronic hemodialysis (CHD) [2, 3]. VKAs are approved for use in patients with AF and CKD S5/S5(D) with recommendations for individual risk assessment; an important condition for efficacy and safety is the patient's stay ⩾70% of the time in the recommended INR range. It has been noted that more severe stages of CKD are associated with a decrease in the period of INR stay in the therapeutic range [37, 38]. VKA can lead to CKD/exacerbation of CKD stage as a result of recurrent subclinical glomerular hemorrhages or accelerated tissue

and vascular calcification [37–39]. Available information on the efficacy and safety of VKA use in patients with AF and CKD S5/S5(D) is conflicting, and there are no large RCTs [37]. The results of a prospective study evaluating hemorrhagic and thrombotic risks with VKAs versus no anticoagulants in patients with AF and CKD on CGD are pending (AVKDIAL, NCT02886962). According to Russian clinical guidelines 2020, the decision on the need for OAC and the choice of an anticoagulant in patients with S5/S5(D) CKD should be made by a multidisciplinary team of specialists, taking into account all the characteristics of the patient. If, during warfarin therapy, INR values are often outside the target range (TRT < 70%), the possibility of prescribing DOACs should be discussed [2]. Experts participating in the KDIGO 2016 consensus conference suggest the use of apixaban at a reduced dose of 2.5 mg twice daily in CKD S5/S5(D) [6]. Apixaban is also licensed in some European countries for the prevention of stroke/SE in patients with S5/S5(D) CKD at a reduced dose of 2.5 mg twice daily [9]. The US FDA approved the use of apixaban 5 mg twice daily (with dose reduction if necessary) and rivaroxaban 15 mg twice daily in CKD S5 and CKD S5(D) based on limited pharmacokinetic and pharmacodynamic data without clinical data security [6]. Recently, the results of small RCTs have appeared, indicating a comparable safety with warfarin for the use of apixaban in patients with CC < 15 ml/min, or who need chronic hemodialysis.

A South Korean study published in 2023 examined the relative safety and efficacy of DOACs versus warfarin or no OAC in 260 patients with AF and S4/S5(D) CKD from the CODE-AF registry, divided into 3 equivalent group, with a median follow-up of 24 months. [10]. Serious/clinically significant bleeding happened less often in the DOAC group compared to the warfarin group (*RR* = 0.11; 95% CI 0.01–0.93; *p* = 0.043). There were also fewer adverse outcomes summarizing efficacy (thromboembolic complications, death) in the DOAC group compared to the group without OAC (RR 0.16; 95% CI 0.03-0.91; *p* = 0.039) [10].

An expected prospective RCT AXADIA comparing the efficacy and safety of apiscaban 2.5 mg twice daily with VKA, phenprocoumon (INR 2.0-3.0) was published in 2023 involving 97 patients with CKD S5(D) out of 39 medical centers [9]. Serious or clinically significant bleedings were observed in 45.8% of those treated with apixaban, and insignificantly more often in 51.0% of those treated with phenprocoumon; *RR* = 0.93 (95% CI 0.53–1.65), *p* = 0.157. TEC was also non-significantly more common in those treated with phenprocoumon than with apixaban, 30.6% vs 20.8%, respectively (*p* = 0.51; logarithmic rank). There were no significant differences in individual outcomes when comparing apixaban with phenprocoumon (all-cause mortality, 18.8% vs 24.5%; major bleeding, 10.4% vs 12.2%; myocardial infarction, 4, 2% vs 6.1% respectively). Thus, patients with AF and S5(D) CKD who receive an OAC-VKA or DOAC are still at high risk of cardiovascular complications, with no significant difference (perhaps due to the small number of participants) in safety or efficacy when using apixaban at a dose of 2.5 mg twice daily or phenprocoumon. The authors emphasize the need for larger studies and the development of additional measures to reduce the very high risk of TECs and bleedings in the chronic hemodialysis patient population [9].

Evaluation of kidney function when using DOACs. According to the European and Russian 2020 guidelines for AF, the protocols of the main RCTs for evaluating the efficacy and safety of DOACs, as well as instructions for the use of drugs registered in the Russian Federation, the assessment of kidney function when prescribing DOACs should be carried out by calculating the CC [2, 3]. The most common methods for assessing kidney function in clinical practice are creatinine clearance calculated according to Cockcroft–Gault (CC) and estimated glomerular filtration rate (eGFR) using the MDRD or CKD-EPI formulas [4]. Nephrologists prefer to use eGFR according to the CKD-EPI formula, avoiding the Cockcroft-Gault formula, considering it to overestimate true GFR in advanced CKD, which is in conflict with the documents described above. It was proposed to calculate CC and pCKD in a particular patient and use the lowest value when choosing a dose of DOACs. However, this is not consistent with the indication of the Russian Clinical Guidelines 2020 on AF, which read to use CC to assess kidney function and prescribe a full dose of DOACs, if there are no additional restrictions [2].

A recent study assessed the value of the method of assessing kidney function when prescribing DOACs in patients with AF and CKD for the treatment outcomes of patients enrolled in the ORBIT-AFII program [40]. Dosing was considered inadequate when the use of eGFR rather than CC resulted in lower doses (undertreatment) or higher doses (overtreatment). The primary serious adverse outcome was considered combined cardiovascular death, stroke or SE, new onset heart failure and myocardial infarction. Among 8727 patients in the total registry cohort, there was a correspondence between CC and eGFR in 93.5–93.8% of patients. Among 2184 patients with AF and CKD, the correspondence between CC and eGFR was noted in 79.9–80.7% of cases. A discrepancy between CC and eGFR was noted in 41.9% of rivaroxaban users, 5.7% of dabigatran users, and 4.6% of apixaban users. In 1 year, patients treated with eGFR-adjusted doses of DOACs, as undertreated patients, had significantly more serious cardiovascular and neurological events compared with the group treated with CC-adjusted doses of DOACs (adjusted *RR* = 2.93; 95% CI 1.08–7.92; *p* = 0.03). The authors point out the importance of using the calculation of CC for the selection of the dose of DOACs [40].

Customization of the dose of DOACs based on a different method of determining renal function may be justified, but requires discussion with the participation of nephrologists, cardiologists / arrhythmologists, primary care physicians

and, preferably, clinical pharmacologists to assess the risk/benefit ratio in a particular patient [1].

Left atrial appendage occlusion in CKD. The left atrial appendage (LAA) is considered the site of thrombus formation in most AF-associated cardioembolic strokes. LAA occlusion has emerged as an alternative to OAC for stroke prevention in patients with AF. To date, there are no optimal regimens for the treatment of OAC in patients with AF and ESRD. The effectiveness of LAA occlusion in these patients has also not been proven in prospective RCTs until recently. This year, the results of an expected study evaluating the safety and efficacy of LAA occlusion in patients with ESRD were published [11]. The study included 604 patients from the German multicenter Realworld registry who underwent LAA occlusion, including 57 patients with S5/S5 (D) and 57 with CKD S1/S2. The composite endpoint was the occurrence of IS or transient ischemic attack, SE, and/or major or clinically significant bleeding. Patients with CKD S5/S5(D) were compared with patients with CKD S1/S2. A total of 596 endocardial and 8 epicardial LAA occlusion procedures were performed. The incidence of serious complications was 7.0% (42/604 patients) in the total cohort, 8.8% (5/57 patients) in patients with ESRD and 10.5% (6/57 patients) in a comparable CKD control group S1/S2 ($p = 0.75$). Estimated recurrence-free survival after 500 days was observed in 90.7 ± 4.5% in patients with ESRD and 90.2 ± 5.5% in a comparable control group ($p = 0.33$). Thus, the study showed that the LAA occlusion procedure can be the method of choice for medium-high risk of stroke in patients with CKD, including those with contraindications to long-term use of NOACs [11].

Treatment strategy for patients with atrial fibrillation and chronic kidney disease

For the treatment of patients with AF and CKD, as well as patients with AF in the general population, two alternative therapeutic strategies are recommended: 1) rate control; 2) heart rythm control. Treatment is carried out in order to reduce the severity of AF symptoms, improve hemodynamic parameters, and prevent possible complications [2, 3, 6].

The strategies of "rate control" and "rhythm control" in the treatment of patients with AF are equivalent in reducing the risks of development and progression of heart failure, readmissions, deaths from cardiovascular and other causes. When choosing antiarrhythmic therapy (AAT) — the "rhythm control" strategy, the goal is to reduce the symptoms of AF, and not improve the prognosis of health and life. In patients without a clear indication for rhythm control, the "rate control" strategy should be followed by default. The indications for choosing a rhythm control strategy in patients with CKD are similar to those in patients in the general population [6]. "Renal" factors in favor of the "rhythm control" strategy are presented in Fig. 2.

Frequency control. The main indication for choosing heart rate control in CKD is the presence of a structural heart lesion. β-blockers, veropamil/diltiazem, digoxin are used. In CKD, water-soluble drugs should be avoided, since they can accumulate in the body due to a decrease in renal excretion (atenolol and sotalol), it is necessary to adjust the dose of drugs with a mixed metabolism (bisoprolol). In patients with CKD, it is preferable to prescribe lipophilic

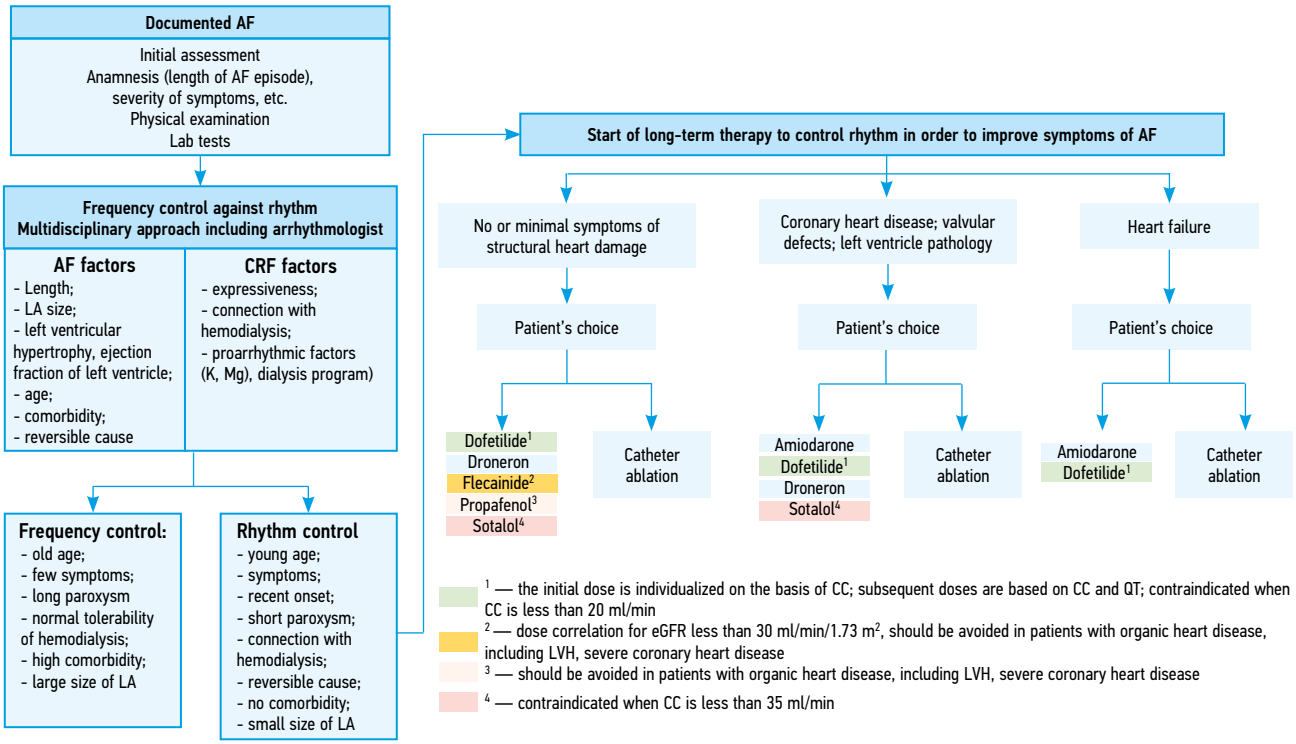

Fig. 2. Decision-making algorithm for frequency control or rhythm control in chronic kidney disease (CKD). AF — atrial fibrillation; LA — left atrium; CRF — chronic renal failure; LVH — left ventricular hypertrophy (Adapted from [6])

drugs that are metabolized in the liver (such as metoprolol and carvedilol) [2, 6].

The results of a cohort study evaluating the risk of using digoxin in patients with CKD for the treatment of AF and heart failure, which included a total of 31.933 patients with CKD, showed that all-cause mortality was higher in the digoxin group than in the non-digoxin group [41]. In cases where medical therapy does not control the ventricular rate, ablation of the AV junction and implantation of a pacemaker (pacer) should be considered. However, the high incidence of complications with transvenous access of the pacemaker in patients on hemodialysis limits the use of this method [6].

Rhythm control. Direct current cardioversion (DCVC) is more effective in restoring sinus rhythm than antiarrhythmic drugs, and, unlike most antiarrhythmic drugs, does not depend on kidney function (Fig. 2). However, the risk of AF recurrence is higher as the stage of CKD worsens; on the other hand, CKD patients who remain in sinus rhythm show improvement in renal function. The use of class IA (disopyramide, quinidine), IC (flecainide, propafenone) and class III (dofetilide, dronedarone, sotalol) rhythm control agents in patients with CKD is limited in those with decreased renal clearance and structural heart damage due to proarrhythmic risks. It remains unknown whether or not there is more pronounced organ toxicity of amiodarone in patients with chronic renal failure. Catheter ablation to maintain sinus rhythm is more effective than antiarrhythmic drugs alone in patients with CKD, as in the general population [2, 6].

CONCLUSIONS

An increase in the number of patients with both AF and CKD is expected, including patients with AF on hemodialysis. The coexistence of both conditions leads to an increased risk of both thromboembolism and hemorrhage, and which is especially high among patients with ESRD receiving hemodialysis. The substrate for AF is atrial cardiomyopathy, with structural, electrophysiological, and molecular atrial remodeling. The study of the pathogenesis of AF at the molecular level has begun recently. Understanding the biological pathways of the pathogenesis of AF may help in the future to develop new approaches to the treatment of both patients with AF and CKD, and AF in the general population.

Currently, among patients with ESRD, the methods of TEC prophylaxis and treatment strategies are being introduced, and the evidence base for their use among patients with S4/S5 CKD, including patients on hemodialysis, is being gathered, which requires large-scale RCTs.

ADDITIONAL INFORMATION

Competing interests. The authors declare that they have no competing interests.

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