Acute coronary syndrome in patients with atrial fibrillation: the possibilities of modern anticoagulants

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Abstract

Review of the literature shows modern approaches to prescription of oral anticoagulants in patients with atrial fibrillation in the development of acute coronary syndrome. This clinical situation requires a comb of two antiplatelet drugs in combination with an anticoagulant, dramatically increasing the risk of bleeding. In accordance with the accumulated scientific data and international guidelines the basic approaches to the treatment of patients at different stages of the disease are generalized.

Key words: atrial fibrillation, acute coronary syndrome, platelet antiaggregants, anticoagulants.

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Острый коронарный синдром у пациентов с фибрилляцией предсердий: возможности использования современных антикоагулянтов

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Резюме

В статье приведены обзорные данные, которые освещают современные подходы к назначению пероральных антикоагулянтов у больных фибрилляцией предсердий при развитии острого коронарного синдрома. В данной клинической ситуации необходима комбинация двух антиагрегантных

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препаратов в сочетании с антикоагулянтом, драматически увеличивающая риск кровотечений. В соответствии с накопленными научными данными и международными рекомендациями обобщены основные подходы к лечению больных на разных стадиях заболевания.

Ключевые слова: фибрилляция предсердий, острый коронарный синдром, антиагреганты, антикоагулянты.

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Introduction

Atrial fibrillation (AF) is the most prevalent type of heart rhythm disturbance in clinical practice. It is related to the increase in death rate (total and cardiovascular mortality and sudden death), stroke risk and systemic thromboembolism, heart failure, acute coronary syndromes (ACS), and life quality worsening [1].

AF is diagnosed in every fifth patient admitted to the hospital due to ACS [2]. There is a two-fold increase in 30-day mortality in patients with ACS and AF onset in comparison with patients with sinus rhythm [3]. A meta-analysis demonstrated that AF had a significant additional impact on mortality in ACS patients even when adjusted for the main risk factors [age, hypertension (HTN), diabetes mellitus]: pre-existent arrhythmia — 28%, acute onset arrhythmia — 37% [4].

The treatment of ACS and AF has progressed a lot in the last years, and evidence-based guidelines were proposed for the treatment of these diseases [5, 6].

A major part of these recommendation concerns the improving of oral anticoagulant and antiplatelet treatment for the safe and efficient decrease of thromboembolism risk. The prevention of the last one is an important part of treatment approach [7].

Vitamin antagonists have been used for almost 60 years, and now novel oral anticoagulation medications (NOAC) with different mechanisms of action are approved for thromboembolism prevention worldwide, including Russia. Thromboembolic disorders should be approached carefully in management of AF and ACS patients. Compared to warfarin and its analogues, the direct thrombin and Xa factor inhibitors have better pharmacological profile. They act directly and independently from antithrombin III level, and are small molecules with predictable pharmacodynamics. This enables 1–2 intake/day (in fixed doses) without any regular control of the anticoagulant effect. The direct thrombin and Xa factor inhibition by oral anticoagulants became a warfarin alternative.

Long-term antiplatelet and anticoagulant therapy showed its advantages in the prevention of thrombotic and thromboembolic events. However, the difficulties arise in case of co-existent indications for both antiplatelet drugs and anticoagulants in a single patient. Will this combination therapy provide additional benefits or will it increase the hemorrhage risk?

Such sophisticated clinical situations are discussed in updated practical guidelines. Nevertheless the final decision should be made with the regard to all the advantages and risks of an aggressive antithrombotic approach. Existent evidence is rather contradictory and has lots of "black spots". Many trials show notable increase in hemorrhage risk without higher efficiency.

Our review suggests modern understanding about the opportunities of anticoagulant and antiplatelet therapy in ACS patients with AF.

Modern preventive approaches in patients with atrial fibrillation and systemic thromboembolism

After the publication of the Recommendations of All-Russian Scientific Society of Cardiology (RSSC) and the All-Russian Scientific Society arrhythmology (RSSA) on diagnosis and treatment of AF in 2011, there have been significant changes in the approaches to prevention of stroke and systemic (arterial) thromboembolism in patients with AF. This is mostly due to the publication of the results of two large clinical trials — ARISTOTLE and ROCKET-AF [8, 9].

Based on the results of these two studies the list of NOAC for stroke and systemic embolism prevention in patients with AF could be broadened. In 2012, an updated consensus to the recommendations of the European Society of Cardiology (European Society of Cardiology, ESC) was published [10].

The European experts emphasize a direct relation between the CHA2DS2-VASc score and the probability of stroke development in patients with AF, additional risk factors, as well as the necessity of long-term (life-long) oral anticoagulation therapy for patients at high risk. In accordance with these ESC recommendations, patients with AF and valvular heart disease should be given vitamin K antagonists (VKA). Patients without valvular disease even if there is 1 point on a scale of stroke risk assessment CHA2DS2-VASc should get anticoagulation therapy by NOAC. In addition, in April 2013, European Heart Rhythm Association (EHRA) has published practical guidelines on NOAK use for the treatment of non-valvular AF, in specific clinical situations [11].

The guidelines discuss the use of three drugs approved in the European Union and the United States for the prevention of thromboembolic complications in patients with non-valvular AF, namely:

Dabigatran, a direct thrombin inhibitor, in a dose 150 and 110 mg twice daily, the key study RE-LY;

Rivaroxaban, a factor Xa inhibitor, in a dose 20 and 15 mg once daily, the key study ROCKET-AF;

Apixaban, a factor Xa inhibitor, in a dose 5 and 2.5 mg twice daily, the key studies ARISTOTLE and AVERROES.

The updated guidelines for the treatment of AF ESC point that NOAC have certain advantages compared to warfarin.

Novel recommendations for the treatment of AF by the American Heart Association (AHA), American College of Cardiology (ACC) and Heart Rhythm Society (HRS) in collaboration with the Society of Thoracic Surgery were published March 28, 2014 in the journals JACC, Circulation and Heart Rhythm [12], replacing previously published recommendations 2006 [13] updated in 2011 [14, 15]. They also include some changes of the European guidelines 2012 [10].

The guidelines indicate how to treat the majority of patients with AF; including a more detailed calculator for the stroke risk assessment in patients with non-valvular AF. The scale CHADS2 is changed to a more comprehensive one CHA2DS2-VASc. The indications for acetylsalicylic acid (ASA) and NOAC are listed.

ASA use is associated with the small but definite risk of bleeding, and many studies have shown either no benefit or a slight benefit in reducing the risk of thromboembolic complications.

The previous guidelines recommended only warfarin anticoagulation, whereas recommendations 2014 include three novel anticoagulants for the treatment of non-valvular AF. Oral anticoagulants are recommended for patients with non-valvular AF and prior stroke, transient ischemic attack (TIA) or CHA2DS2-VASc score 2 or higher. The following options are recommended: Warfarin (under the control of the international normalized ratio, INR, within the range 2.0–3.0) (level of evidence A), dabigatran etexilate (level of evidence B), rivaroxaban (level of evidence B), and apixaban (level of evidence B).

Dabigatran and rivaroxaban are contraindicated in patients with end-stage renal failure and those undergoing hemodialysis. However, apixaban is approved for patients on hemodialysis.

Barriers to widespread use NOAC is the high cost of these drugs.

Antithrombotic therapy in patients with atrial fibrillation in acute coronary syndromes

Thrombosis of the coronary arteries is the cause of 95% macrofocal myocardial infarctions. The intracardiac thrombosis (particularly thrombosis of the left atrial auricle), which is detected in approximately 30% of patients with AF, often leads to ischemic stroke. AF can be considered one of the most common cardiac pathology leading to thrombosis.

The frequency of adverse outcomes (death, myocardial infarction, as well as the recurrent myocardial ischemia requiring revascularization) in patients survived ACS remains high for quite a long time, even with modern, advanced treatment [16, 17].

Therefore ACS patients require more intensive antithrombotic therapy for 1 year after the cardiovascular event. If no reoccurrence has happened during this period, it suggests that coronary heart disease (CHD) is stabilized, and antithrombotic exposure can be diminished [18–21].

The key factors should be considered when selecting the optimal duration and components of antithrombotic therapy in patients with CHD

and AF:

- the risk of thromboembolic compli-cations assessed according to the scale CHA2DS2-VASc;
- the risk of bleeding according to the scale HAS-BLED;
- presence/type of implanted stent and the prescription of percutaneous coronary intervention (PCI);
- CHD course (stable or ACS);
- the risk of death within 6 months according to the scale GRACE in ACS patients.

There is a number of significant issues regarding antithrombotic treatment in both early and remote follow-up of patients with ACS and AF. First of all, it concerns the need for the simultaneous use of oral anticoagulants and antiplatelet agents, which significantly increases the risk of major bleeding. The novel antiplatelet drugs (prasugrel, ticagrelor) for the treatment of patients with ACS led to the further complications of the existing situation.

Current guidelines indicate the prescription of a loading dose (150–300 mg) of ASA (in the absence of contraindications) and P2Y12 platelet receptor blocker (clopidogrel, ticagrelor or prasugrel) as soon as possible in patients with ACS. A parenteral administration of anticoagulants (bivalirudin, unfractionated heparin, fondaparinux or enoxaparin) must be also initiated.

In patients with AF, constantly taking oral anticoagulants, who developed ST elevation ACS, myocardial reperfusion by a primary PCI performed through the radial artery access is the treatment of choice. Besides this, if the patient is constantly receiving VKA, PCI is recommended with its ongoing administration.

The therapeutic values of INR is considered a relative contraindication to thrombolytic therapy, and the higher the INR, the greater the risk of bleeding. Obviously, when fibrinolytic is decided to be administered, parenteral anticoagulants should not be used. The effect of the later ones is considered non-significant in patients receiving VKA at INR below 1.5. In this case it is possible to follow standard approaches in ACS patients. In these patients a controlled anticoagulation method is more reasonable (in particular, intravenous infusion of non-fractionated heparin), as it has fewer problems if clinically significant bleeding occurs. There is evidence that angioplasty/stenting of the coronary arteries is safe without parenteral anticoagulants within therapeutic INR (2 to 3).

Approaches to early treatment of ST-segment elevation ACS in patients receiving NOAC are not developed; and their withdrawal is recommended before performing PCI.

If thrombolytic therapy is the only option for reperfusion, constant VKA intake is a relative contraindication. The administration of parenteral anticoagulants should be postponed until INR reduces below 1.8 (for patients receiving VKA), or until the elimination of NOAC (at least 12 hours after the last dose). In patients treated by NOAC, thrombolytic therapy is possible only if some coagulation parameters are within the normal range: activated partial thromboplastin time (aPTT), thrombin time in the dilution or ekarin clotting time for dabigatran etexilate; prothrombin time, or the anti-Xa activity test for both rivaroxaban and apixaban [22, 23].

If non-ST-elevation ACS develops in a patient with AF who is constantly receiving oral anticoagulants, the treatment strategy, including antithrombotic, will largely depend on the mortality risk measured by the GRACE scale (or other risk assessment scale), and bleeding risk by a scale CRUSADE [24, 25].

In very high risk (assessed by GRACE scale) patients with non-ST-segment elevation (when the urgent invasive strategy must be applied, namely PCI within 120 minutes after first contact with the medical staff) the approaches are the same as in patients with ST-elevation ASC. However, thrombolytic therapy is contraindicated in case of NOAC intake.

In patients with high (more than 140 points by GRACE scale) and intermediate risk (109–140 points by GRACE scale) coronary angiography and PCI can be delayed for 24–72 hours. In most cases, this will be enough for anticoagulant elimination and for INR reduction below 1.8 in case of VKA intake. Parenteral anticoagulants should not be administered before INR reduces below 1.8 (for patients receiving VKA), or until cessation of NPOAK effects (at least 12 hours after the last dose).

Patients survived an ACS (both ST-segment elevation and non-ST-segment elevation), regardless of the chosen approach (PCI or medication treatment) should take combination

antiplatelet therapy including ASA and one of the platelet receptor P2Y12 blockers (clopidogrel, ticagrelor or prasugrel) for 12 months.

Combination of ASA and VKA when the target INR 2.0–2.5 is achieved is known to be superior to ASA monotherapy regarding secondary prevention of coronary thrombosis. In patients with low to moderate risk of bleeding, the benefits of such an approach outweigh the risk of hemorrhages. Monotherapy by VKA with target INR (2.8–4.2) achievement is more efficient compared to ASA. In this case the risk of bleeding is lower than in combination ASA + VKA (with target INR 2.0–2.5). At a lower level of anticoagulation and in case of poor INR VKA demonstrate low efficiency for secondary prevention of coronary thrombosis.

However, a "triple antithrombotic therapy" is required in some cases. This include simultaneous use of oral anticoagulants and double antiplatelet therapy (ASA in combination with one of the P2Y12 platelet receptor blockers) and is associated with the higher risk of major bleeding. Therefore, the doctors should minimize the period of the "triple therapy", and to minimize the risk of major bleeding in the period of its administration. The following precautions are recommended:

- access for PCI through a radialis;
- low-dose ASA (75–100 mg daily);
- to maintain low doses of VKA (target level of INR 2.0–2.5) or to administer an NOAC;
- to use bare metal (uncoated) stents rather than drug-eluting stents.

Today a combination of VKA (warfarin), ASA and clopidogrel is the most clinically used "triple antithrombotic therapy". The efficacy and safety of the combination of VKA with the new antiplatelet agents (ticagrelor, prasugrel) and NOAC with antiplatelet agents have not been studied.

Moreover, there is evidence that "dual antithrombotic therapy" is as effective (a combination of clopidogrel with VKA) as "triple antithrombotic therapy" (combination of VKA with ASA and clopidogrel) regarding the prevention of death, myocardial infarction and stroke. At the same time it is accompanied by a 2-fold reduction in the incidence of major bleeding. So long "triple antithrombotic therapy" is not always required, and in some patients "dual therapy" (VKA and one antiplatelet agent) is enough. However, it is still not decided whether the antiplatelet agent should be ASA or clopidogrel [26].

Special clinical studies evaluating the optimal duration of the "triple antithrombotic therapy" in patients with AF who underwent ACS have not been conducted. It is also unknown whether the duration should vary depending on the chosen treatment strategy (PCI or medication therapy).

When performing elective PCI in patients with AF, the bare metal stents should be preferred, unless drug-eluting stents are much more beneficial (long stenosis, small diameter arteries, diabetes mellitus, and others).

Bare metal (uncoated) stents require 1-month "triple antithrombotic therapy", and then over the next 11 months "dual therapy" must be continued (a combination of oral anticoagulant and antiplatelet drug, e. g. preferably, clopidogrel and VKA). After 12 months antithrombotic therapy may include only one oral anticoagulation drug [27].

Oral anticoagulation monotherapy (preferably VKA) after 1 month of "triple therapy" might be considered in patients with a high risk of bleeding by HAS-BLED scale (> 3 points) and low (< 8 %) risk of death within 6 months after ACS by GRACE scale (< 118 points). In patients with high (> 8 %) risk of death within 6 months after ACS by GRACE scale (> 118 points) and low risk of bleeding by HAS-BLED scale (< 3 points) "dual therapy" can be extended up to 6–12 months.

The discontinuation of clopidogrel and switching to ASA monotherapy can contribute to the relapse of the disease, in particularly, to the increase in the frequency of coronary events in the next 3 months [28].

However, there are patients in whom the combination of ASA with platelet P2Y12 receptor blocker is not applicable either due to the ASA intolerance and/or failure to use it with any of the approved platelet P2Y12 receptor blocker. Moreover, a number of diseases require long-term administration of anticoagulants, which cannot be replaced by antiplatelet agents, for instance, AF requires a lifelong anticoagulation therapy [29–33].

Since long-term use of parenteral anticoagulants (heparins) is not possible due to the inconvenience (they are used in pregnancy, in patients with neoplasms and venous thromboembolic complications, as well as in perioperative surgical interventions with an increased risk of bleeding),

oral anticoagulation (VKA) agents are of high importance. Warfarin is the most studied and most commonly used in this group [34–36].

In patients with AF and venous thromboembolic complications 1 year after ACS monotherapy with NPOAK (without ASA) can be administered in combination with gastroprotective drugs (proton pump inhibitors/H2 blockers/antacids) [31].

Growing evidence speaks favors administration of clopidogrel rather than ASA in combination with VKA. In patients with a high risk of bleeding triple antithrombotic therapy can be reduced to 4 weeks after bare metal stents implantation.

At high risk of bleeding fondaparinux is an alternative option in case of PCI (in non-ST-elevation ACS).

Novel oral anticoagulants in the prevention of thromboembolic events in patients with atrial fibrillation and acute coronary syndrome: a component of the combination antithrombotic therapy

The results of a multicenter randomized trial studying the efficiency of NOAC dabigatran [37], rivaroxaban [38], apixaban [39] and edoksaban [40] vs. warfarin in patients with AF have been published in the last 5 years. NOAc were shown to be as effective as warfarin in preventing recurrent arterial embolism, at the same time being beneficial regarding the lower risk of intracranial bleeding [10–13]. Based on these results dabigatran 150 mg or 110 mg twice daily, rivaroxaban 20 mg per day and apixaban 5 mg twice daily were approved for patients with non-valvular AF in most countries, including the Russian Federation [5].

In the only study showing benefits of NOAC regarding prevention of the coronary atherothrombotic complications low-dose rivaroxaban was administered in a combination with ASA or combination ASA with clopidogrel [34].

Current existing evidence is not sufficient to make any conclusions about the advantages of any particular NOAC and to suggest practice guidelines for NOAC use in patients with CHD.

Based on the results of ATLAS-ACS-TIMI 51, a new indication for rivaroxaban was registered in Russia: the reduction of cardiovascular mortality and relapsing myocardial infarction in combination with ASA and clopidogrel after ACS [40].

In stable CHD and the absence of disease exacerbations oral anticoagulant monotherapy is recommended in patients with AF. However, according to the EHRA recommendations [11], dabigatran (in low doses) should be better combined with ASA in patients with high cardiovascular risk. At the same time, rivaroxaban due to the reduction of coronary risk does not require additional ASA. In 2012, a meta-analysis including the results of 28 randomized clinical trials of NOAC was published [37]. Based on the data, inhibitors of factor Xa (rivaroxaban and to less extent apixaban) are preferred compared to direct thrombin inhibitors.

Based on the study ATLAS ACS 2-TIMI 51, stabilized moderate-high patients with ACS and low risk of bleeding (apparently, old age, moderate renal insufficiency) are the potential candidates for combination of ASA and clopidogrel with the very low doses of rivaroxaban (2.5 mg twice daily) after the withdrawal of the standard parenteral anticoagulants. These are pateints without stroke or TIA, AF, with creatinine clearance of more than 30 ml/min, without any significant liver disease, who do not take regularly inhibitors of cytochrome P450 3A4 and P-glycoprotein [38].

Relatively high-dose NOAC are shown to be equal to warfarin (at target INR of 2–3) regarding the prevention of AF-associated cardioembolic complications [34, 39].

Currently, all NOACs are approved as a monotherapy for the patients with non-valvular AF 1 year after ACS [20].

However, based on the available data, there is no opportunity to suggest their earlier administration after CHD exacerbation.

It was shown that possessing comparable efficacy dabigatran 110 mg twice daily was associated with the lowest risk of bleeding. These data can be regarded as evidence favoring the potential use of dabigatran instead of VKA when triple antiplatelet therapy is indicated after PCI in ACS. This could provide equal to warfarin degree of cardioembolic prevention with the higher safety regarding risk of bleeding [8].

It is worth to note that none of NOACs has a specific antidote. Fresh-frozen blood plasma or concentrated prothrombin complex could be used in case of bleeding. An important factor is time due to the relatively short half-life of NOACs (8–17 hours) [5].

The change from one oral anticoagulant to another

When switching from one oral anticoagulant to another it is extremely important to maintain an adequate level of anticoagulation as well as minimal risk of bleeding [5].

In case of previous VKA intake NOAC can be started as soon as INR falls below 2 because all NOAC are characterized by rapid onset of anticoagulation effect (so, the main point is to coordinate the vanishing warfarin effects and increasing anticoagulant effect of NOAC). When INR is within the range 2–2.5, NOAC should be started next day; when INR is above 2.5, it is better to check it in 36–42 hours (if warfarin had been taken), and then make a decision on NOAC.

The change from NOAC to VKA may take up to 5–10 days due to the slow onset and end of the VKA action. Thus, NOAC and VKA may be administered simultaneously for a short period of time requiring to achieve therapeutic range of INR. Since NPOAK may influence the INR level (in particular, factor Xa blockers — apixaban and rivaroxaban), it is important to follow few rules when they are administered together:

a) to control INR immediately before the next NOAC dose intake;

b) to control INR 24 hours after the last dose of NOAC (thus, when only VKA are taken).

INR control is also recommended during the first month after the switch to VKA from NOAC until INR is stabilized at the level 2–3 at a minimum of three consecutive determination procedures.

The transition from one NOAC to another can be performed simultaneously: according to the timetable a new NOAC is taken at the appropriate time.

In case of heparin therapy NOAC can be administered immediately after the cessation of intravenous infusion of unfractionated heparin, whose half-life is 2 hours.

In case of low/molecular weight heparines (LMWH) first dose of NOAC should be administered at the time of the next scheduled administration of LMWH.

Adherence and precise therapy regimen are the key factors when NOAC are prescribed because they have a relatively short half-life, and missing more than one dose leaves the patient unprotected.

Conclusions

Current approaches to the patients with ACS have recently significantly changed and imply early myocardial revascularization, active antithrombotic therapy that leads to the reduction of the cardiovascular complications. However, the optimal approaches to the antithrombotic therapy in patients with ACS and AF are not currently developed.

In recent years, oral anticoagulation and antiplatelet therapy for the prevention of AF-associated thrombotic events has broadened. New drugs with the different mechanisms of action (apixaban, dabigatran, rivaroxaban) have more predictable pharmacological profile, show lower risk of bleeding and lower variability between patients. No need for routine monitoring of biochemical parameters could improve patient adherence.

Further comparison studies are required for a comprehensive assessment of the effectiveness of new antiplatelet and anticoagulant agents and the benefits of the regimens in patients with ACS and AF.

Currently there are no studies demonstrating, which agent is better and safer or preferable in special clinical situations. Therefore, now every medical doctor can rely on available meta-analyses and indirect comparison trials when making decision in a special situation requiring thromboembolic prevention in a patient with non-valvular AF.

Conflict of interest

The authors declare no conflict of interest.

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