ENGLISH VERSION: ANTITHROMBOTIC THERAPY IN PREVENTION OF CARDIOVASCULAR EVENTS (DEATH, ACUTE MYOCARDIAL INFARCTION, STROKE) IN PATIENTS WITH CHRONIC HEART FAILURE*

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Chronic heart failure is one of the main clinical challenges of modern medicine. The present paper discusses the features of antithrombotic therapy in prevention of cardiovascular events (death, acute myocardial infarction, stroke) in patients with chronic heart failure. It has been specified, which anticoagulants or antiplatelet agents have advantages taking into account the features of the functioning of organs and systems in patients with heart failure. Antithrombotic therapy is indicated for all patients with atrial fibrillation and heart failure. The feasibility of anticoagulant or antithrombotic therapy has not been proven in patients with sinus rhythm, since the risk of bleeding exceeds the antithrombotic effect in patients of this group. The results of controlled trials recommend anticoagulant therapy for patients with heart failure who are at high risk, particularly in atrial fibrillation, with previous thromboembolic episodes, a significant reduction in the left ventricular ejection fraction, intracardiac thrombosis and in patients with aneurysm. There is also no evidence to prescribe antithrombotic therapy for reducing the risk of stroke and thromboembolism in patients with heart failure and sinus rhythm. The choice of antithrombotic therapy should be guided by the CHA_2DS_2-VASc and HAS-BLAD indices.

Key words: antithrombotic therapy, prevention of vascular events, chronic heart failure

Introduction

Chronic heart failure (HF) is one of the main clinical problems of modern medicine, affecting 1-2% of the adult population and 6-10% of people above the age of 65 [13]. In Ukraine, the prevalence of HF among the adult population is 1.7% [1]. HF causes 5% of all hospitalizations, including geriatric ones. Mortality among hospitalized patients with heart failure is 4% per month, 18% per 6 months, 30% per year and 40% per 3 years.

Based on world statistics, it can be assumed that in Ukraine there are approximately 480-560 thousands of patients with HF [2].

After atrial fibrillation (AF), which is responsible for 15% of strokes, HF is the next most common cause (9%) of all strokes.

Cardioembolic strokes, myocardial infarction (MI), sudden death and venous thromboembolism occupy up to 30% in the structure of fatal and nonfatal complications in patients with HF and cause high rates of mortality and hospitalization [21]. In this context, antithrombotic therapy (ATT) is very promising [10].

Of particular importance is ATT in AF, which is the most frequent arrhythmia that occurs at a frequency of 1%-2% in the general population: 0.5% in individuals aged 40-50 years and 5%-15% in people above the age of 80 [7]. Stroke is the most common complication of AF. In the Framingham study, the risk of stroke in AF was by 5 times higher than in individuals with sinus rhythm and increased up to 1.5% at the age of 50-59 years and up to 23.5% at the age 80-89 years. 70-80% of persons with AF have indications for treatment with oral anticoagulants (OAC), 20-30% of them suffer from coronary heart disease. In patients with AF, warfarin and antiplatelet agents reduce the risk of stroke by approximately 65% and 20%, respectively.

Epidemiological studies indicate that 29% of patients with HF do not receive ATT, 31% receive only ineffective ATT and 39% receive warfarin, of which only 10% maintain INR within the therapeutic interval [8].

Reassessing the risk of bleeding is a barrier for prescribing ATT by therapists. The risk of bleeding increases with age, but the protective effect of ATT exceeds it in all age groups [20].

In recent years, many new antithrombotic drugs have appeared which have successfully undergone randomized clinical trials (CTs) and have shown high efficacy and sufficient safety. These drugs, as well as the tactics of using ATT, have been subject to serious changes, reflected in the new recommendations of the European and American associations of cardiologists and cardiac surgeons [3, 6, 11], which are still not well known to a wide range of Ukrainian therapists. However, there is still insufficient data on DAPT in patients with HF [19].

Points of application and classification of antiplatelet drugs.

Antiplatelet agents include:

- inhibitors of cyclooxygenase 1, primarily aspirin (acetylsalicylic acid (ASA)) and other non-steroidal anti-inflammatory drugs, which prevents the formation of TxA2 and induced platelet aggregation;
- $R2Y_{12}$ platelet receptors blockers: ticlopidine, clopidogrel, prasugrel, cangrelor; ticagrelor;
- inhibitors of the activation of glycoprotein IIb/IIIa platelet receptors: absiximab, eptifibatide, tirofiban and vorapaxar, inhibiting protease-activating receptor-1.

Anticoagulant strategies include:

- warfarin and other coumarin derivatives that act by blocking the synthesis of vitamin K in the liver.
- indirect thrombin inhibitors: heparin, its low molecular weight fragments requiring a cofactor − antithrombin III;
- direct thrombin inhibitors: hirudin, bivalirudin and dabigatran,
- Xa factor inhibitors: apicosan, edoxaban, rivaroxaban;

Dabigatran (DBG), apixaban, edoxaban, and rivaroxaban (RRB) are referred to as “new anticoagulants” (NAC), often considered in meta-analyzes together.

Antithrombotic therapy (ATT). Despite the frequent prescription to patients with HF, ACC does not effectively prevent thrombosis in HF.

In the WASH clinical trial, it was shown that at a dose of 300 mg, ACC did not reduce the mortality of patients with HF as compared with placebo, increasing the incidence of bleeding from 5% to 13%. In the V-HeFT I and V-HeFT II clinical trials, ACC did not reduce the frequency of thromboembolic events (TEE) in patients with HF. In

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contrast, in the retrospective study CI SAVE, there was a significant effect of ACC in preventing TEE – reduction by 56%, and in the SOLVD clinical trial, by 23% in men and 53% in women, as well as reduction of sudden death by 24%. ACC can contribute to the development of decompensation of heart failure. This is indicated by the clinical trial, which showed a higher incidence of hospitalization of patients treated with aspirin than with warfarin. This is because ACC inhibits the synthesis of vasodilating prostaglandins and increases endothelin-dependent vasoconstriction. This explains the high mortality of patients receiving combined therapy with large doses of ACC and angiotensin-converting enzyme inhibitors, as observed in the WASH, WATCH, SOLVD, and CONSENSUS II clinical trials.

P2Y12 platelet receptor inhibitors of thienopyridine nature (ticlopidine, clopidogrel, prasugrel, ticagreol). Among $P2Y_{12}$ receptor blockers, clopidogrel is the most studied. It is related to thienopyridine group, whose metabolites, formed in the liver involving cytochrome P450, irreversibly block P2Y12 receptors. Ticlopidine and prasugrel reversibly block P2Y12. They act faster and stronger than clopidogrel, but cause more bleeding. Ticagrelor is a derivative of cyclopentyl triazolo-pyrimidines.

Double antiplatelet therapy (DAPT). It has been shown that the double blockade of cyclooxygenase-1 with ACC and P2Y12 ADP receptors with clopidogrel is associated with a significant reduction in the risk of AF. With regard to the risk of stroke, the data is less certain. The PLATO trial demonstrates the advantages of ticagreolol over clopidogrel in preventing thromboembolism and death in patients with acute coronary syndrome (ACS), but at the expense increased frequency of major bleeding, especially with the use of large doses of ACC [14].

The MATCH study found no association of DAPT with a reduced risk of stroke, but there was an increase in the risk of life-threatening hemorrhages. In the ESPRIT and PRoFESS studies (ACC + dipyridamole), a 20% reduction in total mortality from all cardiovascular events was found.

Patients with ACS requiring stenting need DAPT with ACC and antagonists of $P2Y_{12}$ TC receptors to ADP [19].

A meta-analysis of available studies showed that ACC therapy reduced the vascular events by 1.5% and the number of strokes and coronary events by 20% with an insignificant statistically increased rate of hemorrhagic stroke. Stronger inhibitors of P2Y12, prasugrel and ticagrelor, lead to a 20% reduction in the risk of ACS, but there remains an unresolved problem of a significant increase in bleeding as compared to clopidogrel. Data on the effect of prasugrel and ticagrelor in HF is not available.

In high-risk populations (diabetes mellitus, senile age, renal failure, previous MI, stroke and stent thrombosis), the number of ischemic complications remains very high. The same groups are characterized by a high risk of bleeding. These data indicate that ischemic complications are mediated not only by TC, and DAPT does not block these pathways. Anticoagulant therapy is used for treatment of such patients.

Antagonists of glycoprotein IIb/IIIa receptors (abciximab, tirofiban, eptifibatide). Glycoprotein IIb/IIIa is a protein appearing in the membrane of TC when activated, which serves as a receptor of collagen and von Willebrand factor. It provides adhesion and aggregation. The blockade of IIb/IIIa glycoprotein prevents adhesion and aggregation of TC by a mechanism that is different from that of ACC and thienopyridines. Currently, three medications are used in clinical practice: abciximab, tirofiban, eptifibatid.

All three medications have a strong antiplatelet effect and are applied only parenterally, mainly in MI, ACS and coronary angioplasty in combination with heparin and ACC.

Anticoagulants. Unfractionated heparin. Heparin is active against factors of internal and general coagulation mechanisms (in particular, IXa, Xa and thrombin); it is an activator of antithrombin III, accelerating the interaction of antithrombin III with thrombin by more than 1000 times. Antithrombin III rapidly (T1/2<0.1 s) inhibits IXa, Xa and thrombin factors at the plasma heparin from of 0.1 to 10 U/ml. The activated partial thrombin time (APTT) and thrombin time (plasma clotting time with addition of thrombin) are prolonged. The Xa factor on the TC surface and thrombin, bound to fibrin, are not inhibited by heparin and antithrombin III.

Heparin begins to act quickly, which allows doctors to use it in venous thrombosis and PE. The duration of treatment is usually 4-5 days. Indirect anticoagulants per os are simultaneously prescribed, since they provide a valid effect by the time of heparin withdrawal. In thrombosis and embolism, recurring against the background of conventional treatment with indirect anticoagulants (for example, in Trousseau's syndrome), a prolonged heparin therapy is conducted. Heparin is also used: in unstable angina and MI; in balloon coronary angioplasty and stent placement; in operations requiring artificial circulation; in some patients with DIC syndrome.

Low molecular weight heparins (LMWH): enoxaparin, dalteparin, ardeparin, supraparin, reviparin, tinzaparin. LMWH is administered subcutaneously 1-2 times a day, they have almost no effect on blood coagulability and laboratory control is usually not needed. Indication for the use of LMWH is the prevention of venous thrombosis and PE. Their effectiveness in venous thrombosis, PE and unstable angina was demonstrated. Treatment with LMWH is less frequently complicated by heparin thrombocytopenia, osteoporosis and bleeding.

Hirudin and bivalirudin. The hirudin polypeptide is found in the saliva of leeches (Hirudo medicinalis). It lowers blood clotting by blocking the active center of thrombin. The effect of hirudin does not depend on antithrombin III, and therefore the medication can be used in patients with its deficiency. Lepirudin and desirudin are analogs of hirudin, produced by genetic engineering methods.

Bivalirudin (BVR). BVR is a strong, specific, reversible, direct thrombin inhibitor, a synthetic derivative of hirudin, which inhibits free and fibrin bound thrombin, and thrombin-induced activation, and TC aggregation. Unlike heparin, BVR does not require cofactor – antithrombin; it does not cause thrombotic thrombocytopenia syndrome and does not activate TC, which makes it an ideal alternative to heparin. Clinical trial demonstrated positive results of BVR use in stable and unstable angina pectoris, myocardial infarction with and without elevation of the ST segment. BVR has fewer side effects than heparin. The meta-analysis of BVR CT, including 14258 patients with ACS receiving BVR DAPT, in comparison with heparin and glycoprotein IIb/IIIA inhibitor, the PREMIER register (Prospective Registry Evaluating Outcomes After Myocardial Infarctions: Events and Recovery) demonstrated a lower risk of death in patients with decreased left ventric-

ular function <35%, a reduction in hospital mortality by 37% in patients with heart failure.

Coumarin derivatives (warfarin phenprocoumon, aicenokuman and other vitamin K antagonists). Anticoagulants of indirect action block the synthesis of vitamin K-dependent factors of blood coagulation (II, V VII, IX b X) in the liver. Unlike anticoagulants of direct action, their effect develops slowly. In the meta-analysis of CTs, warfarin therapy reduced the risk of stroke by 64% and overall mortality by 26% compared with placebo.

In patients with HF and AF, warfarin in a dose providing INR at 2.0-3.0 reduced the risk of stroke by 65% [5]. DAPT cannot compete with warfarin in this regard. The ACTIVE-W clinical trial, which included patients with AF and ≥1 risk factor for stroke, was withdrawn ahead of schedule due to the obvious advantage of warfarin therapy as compared with combination of ACC and clopidogrel without increasing the risk of bleeding [12].

In the meta-analysis of 6 clinical trials on warfarin therapy, conducted from 2002 to 2012, it was found that the risk of stroke is higher in elderly and senile women who have not previously taken warfarin, with stroke or transient ischemic attacks already present, with renal insufficiency prior to administering ACC, but even in the group at the highest risk (previous stroke), the annual risk of recurrent stroke was relatively low (2.5% per year), which confirms the role of OAC (warfarin) as the main means for preventing cardioembolic complications in patients with atrial fibrillation.

However, taking warfarin has many limitations: bleeding, the need to monitor INR and the dose of warfarin, interaction with other drugs metabolized by cytochrome P450, dependence on genetic polymorphism CYP2C9 and VKORC148,49, dietary interactions. This implies that only half of patients who need warfarin therapy receive it. DAPT ACC and clopidogrel is indicated in patients with AF who cannot use warfarin.

New oral anticoagulants (NOAC). NOAC are designed to overcome the disadvantages of warfarin therapy. Direct thrombin inhibitors (gatrans), in particular dabigatran, combine with thrombin and block the conversion of fibrinogen to fibrin and the activation of V, VII, IX factors and TC.

NOAC, which selectively block thrombin (DBG) or Xa factor (PPB or apixaban), have a number of beneficial characteristics: good tolerability, rapid onset of action, minimal interaction with food and medicines, no need for monitoring and dose titration, proven efficacy and low risk of bleeding.

In the meta-analysis of controlled CTs, NOAC reduced mortality by 11% and 12%, systemic embolism by 18% and 23%, intracerebral hemorrhages by 21% and 54%. The annual absolute mortality risk was 2.4% and 2.8% for NOAC, and 3.1% and 3.5% for warfarin.

Four new CTs (RRB, apixaban and edoxaban) did not include patients taking clopidogrel. The combination of DBG with ACC and DAPT (ACC and clopidogrel) had little effect on the efficacy of DBG, while more DBG doses exceeded, and small ones were highly competitive with warfarin in efficacy without increasing the risk of bleeding. This data supports the evidence that ATT with NOAC does not contribute to greater efficacy, but increases the risk of bleeding. Patients with a high risk of bleeding should not use ATT in combination with NOAC. The use of apixoban at a dose of 5 mg 2 times a day, in ARISTOTLE CT, conducted in 18201 patients with AF and ≥ 1 risk factor for stroke, showed a 1.8-year advantage over warfarin in reducing endpoints, ischemia, bleeding and mortality from all causes. Administering ACC did not influence the effect of apixoban, although the relative risk of stroke decreased from 42% to 16% without increasing bleeding. The use of apixoban in the form of monotherapy, or in combination with ASA, was safer than warfarin.

Direct thrombin antagonists (gatrans). Dabigatran (DBG) is a direct thrombin inhibitor for oral therapy. It is an alternative to warfarin, since it has similar efficacy indices but does not require monitoring of INR. In the United States, the approved and authorized antidote is idarucizumab. In the RE-LY study, DBG showed a higher efficacy compared with warfarin in preventing stroke and systemic emboli and an equal risk of major bleeding without affecting the course of heart failure.

Blockers of Xa factor (apixaban, RRB, edoxaban). Apixaban and RRB are the most studied inhibitors of Xa factor. Other inhibitors of Xa factor have been developed and applied in various stages of clinical use: edoxaban, otamixoban, darexoban, betrixaban and TAK-442. Among NOAC, apixaban DBG more effectively prevent strokes than warfarin in patients with non-valvular pathology. An additional advantage of NOAC is no effect of food and other medicines and no need to control the coagulation level by laboratory tests.

APB is recommended by the US National Institute of Health for prevention of stroke and systemic embolism in people with non-valvular AF and at least one of the risk factors (sustained stroke, transient ischemic attack, age of 75 years or above, diabetes and heart failure).

In the ARISTOTLE study, APB better prevented stroke development and systemic embolism in patients with AF. Administering APB demonstrated a less number of major bleeding with less mortality than with warfarin. In this study, one third of patients suffered from heart failure or reduction in left ventricular ejection fraction. In the APPRAISE-2 study − 5 mg APB 2 times a day, in addition to the standard ATT, − there was no reduction of ischemic episodes, but the risk of major bleeding significantly increased in patients with acute coronary syndrome and two additional risk factors of recurrent stroke. The study was withdrawn ahead of schedule due to a large amount of hemorrhages. In this study, 28% of patients suffered from heart failure. Mortality in patients with heart failure, treated with APB, was reduced by 23% as compared with 76 placebo.

In the ROCKET AF study, wherein 60% of patients had HF, RRB was no better than warfarin in preventing stroke, systemic embolism and hemorrhage frequency. Fewer cases of intracranial and fatal bleeding were observed.

In the ATLAS ACS-TIMI 51 study, 10% patients had HF and in this subgroup there were fewer complications than in the placebo group.

Meta-analysis of efficacy and safety in direct anticoagulants 11 clinical trials (DBg, apixoban, edoxaban and RRB) in the prevention of stroke and venous thromboembolism as compared with warfarin in patients above the age of 75 years, suffering from AF, showed that they have at least equal to warfarin effectiveness but varying degrees of safety. DBG 150 mg caused a statistically significant increase in gastrointestinal bleeding, but significantly reduced the number of hemorrhagic strokes. Apixoban and edoxaban reduced the risk of major bleeding, and RRB did not differ from warfarin in terms of safety [18].

Research data on 44563 patients with AF have been published, which showed the absence of NOAC superiority in reducing the incidence of stroke and systemic embolism as compared to warfarin in 21095 patients with heart failure but having such superiority in patients without heart failure [17].

In another meta-analysis ("Direct oral anticoagulants for stroke prevention in patients with atrial fibrillation: meta-analysis by geographic region with a focus on European patients") [9], which included data on 72.963 patients, no advantages of NOAC were detected, as compared to warfarin in terms of efficacy, but a reduced tendency to bleeding was observed.

Method for using ATT in HF. Indications for using ATT in patients with heart failure:

- Atrial fibrillation (AF)
- Severe HF
- Thrombi of the left ventricle after sustained myocardial infarction
- Left ventricular aneurysm
- Acute coronary syndrome
- Previously sustained embolic episodes

ATT risk assessment and bleeding hazard. CHA_2DS_2-VASc and HAS-BLED hazard ratings. Every year, from 2.3% to 6.8% of patients receiving anticoagulants suffer from bleeding. The intensity of anticoagulation, in particular, the combination ATT and anticoagulant therapy, hypertension, previous cerebral ischemia, advanced age are the factors that predispose to bleeding. This data is used for prevention of bleeding.

When choosing a therapy, one should assess the risk of ischemic events and bleeding. To evaluate the possible ischemic events, European Consensus recommends $CHADS_2$ index (cardiac failure, hypertension, age, diabetes mellitus, stroke [doubled]) score). When its value is more than 2, oral anticoagulants are needed. If the index is from 0 to 1, double ATT is preferred.

The new scheme CHA_2DS_2-VASc (Table 1) takes into account more risk factors and risk of stroke in the population [4]. Under this scheme, oral anticoagulants are prescribed at CHA_2DS_2-VASc ≥ 2. When CHA_2DS_2-VASc is 1, ACC is prescribed, and at CHA_2DS_2-VASc – 0, anticoagulants are not prescribed at all.

HAS-BLED scale includes evaluating the risk of bleeding [16] (Table 1).

If the number of risk factors is ≥3, indicating a high risk of bleeding, one should very carefully weigh the benefit / harm ratio in the prescription of ATT. This index effectively predicts the chance of bleeding in patients receiving the triple therapy.

CHADS2 and HAS-BLED risk scores may be useful for personalization and selection of ATT for patie nts with HF and AF [15].

The basic principles of ATT in patients with HF and AF, based on evidence-based medicine

1) Triple therapy should not be used in patients with low risk of stroke, CHA_2DS_2-VASc 0 or 1.

2) Warfarin therapy exceeds DAPT, despite the greater risk of bleeding, but it is important to obtain patient's consent to follow the rules of warfarin administering. Patients being less than 65% of time in the optimal INR zone, have advantages with respect to those receiving DAPT.

ATT in HF patients with sinus rhythm. A large number of randomized clinical trials with ATT and ACT have been conducted in patients with sinus rhythm. It has been found that warfarin reduces stroke more than ACC, but increases the number of hemorrhages. The authors of meta-analyzes concluded the feasibility of ACC in patients at high risk of bleeding, and warfarin with a large number of risk factors for stroke. The use of ATT for prevention of stroke in patients with non-ischemic etiology requires further research.

Conclusion. HF in patients with atrial fibrillation increases the risk of venous thromboembolism, which is less evident in patients with heart failure and sinus rhythm. ATT is indicated to all patients with atrial fibrillation and heart failure. In choosing the ATT, one should be guided by the principles described above, and CHA_2DS_2-VASc and HAS-BLAD indexes. ATT of patients with heart failure is associated with the presence of atherosclerotic vascular lesions. ATT is effective in many forms of heart disease, including patients with HF and AF, but the feasibility of anticoagulant or ATT was not proven in patients with sinus rhythm, although it is shown that heart failure is accompanied by TC activation and hypercoagulation, and there is evidence that warfarin therapy reduces the incidence of stroke in patients with HF. The risk of bleeding exceeds the antithrombotic effect in patients with sinus rhythm. The results of controlled studies do not allow us to recommend anticoagulant therapy for all patients with heart failure, but recommend it to persons at high risk, particularly in AF, with previously sustained thromboembolic episodes, a significant decrease in left ventricular ejection fraction, in intracardiac thromboses and the aneurysm. There is also no evidence to prescribed ATT to lower the risk of stroke and thromboembolism in patients with sinus rhythm. Moreover, ACC is associated with more frequent hospitalization of patients with HF. There is a weak evidence of the reduction in mortality with warfarin application as compared to ACC.

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