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Cardiovascular management in cancer patients with thrombocytopenia

Dynamics of risk factors and cardiovascular diseases: analytical review of international and Russian data for 2017

New EHRA guidelines on anticoagulant therapy in patients with atrial fibrillation: comments of Russian experts

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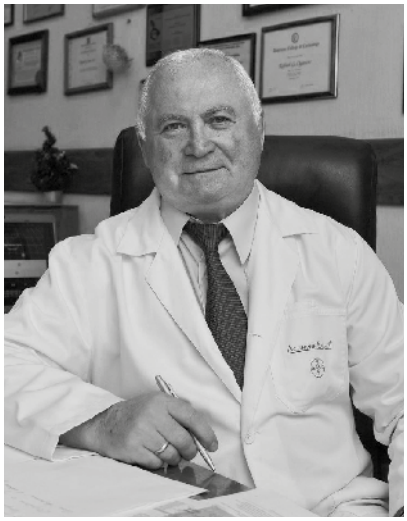

Editor's Welcome

Dear colleagues!

In the 19th issue of the International Heart and Vascular Disease Journal, there are the leading article, original and review articles, the expert opinion section and the report on the results of the ESC Congress 2018.

The "Leading article" section includes a work of a group of American scientists dedicated to the treatment of cardiovascular disease in cancer patients with thrombocytopenia. In particular, the pathophysiological aspects of cancer-associated thrombocytopenia and treatment tactics of such patients with coronary heart disease are reviewed.

The "Original articles" section includes two articles. In the first one the author from Egypt studied the safety of ticagrelor administration in post fibrinolysis patients who had myocardial infarction with ST elevation. This study included 200 patients. According to the author's opinion, in patients below 75 years, delayed prescription of ticagrelor 2h after fibrinolysis was not less safe than administration of clopidogrel in terms of thrombolysis-associated bleeding of various severity. The second article was dedicated to detection of clinical and laboratory characteristics of arterial hypertension in patients with chronic kidney disease, stage 5. For this reason, 248 patients on maintenance hemodialysis therapy were involved in this study. It was observed that long-term duration of dialysis is associated with an increase in the number of patients with arterial hypotension. In addition, it was found that 24h-blood pressure monitoring parameters correlated with electrolyte balance impairment and nitrogen metabolism.

The review article of Professor Mekhman N. Mamedov discusses the dynamics of main risk factors and cardiovascular diseases in Europe. It also analyses the organization of cardiologic medical service and the fight against cardiovascular diseases in Russia. The second article made by Russian authors reviews the characteristics of vascular elasticity, approaches to its evaluation and their prognostic meaning. It included data on the possibility of using these parameters for evaluation of cardiovascular risk and therapy control in different categories of patients.

The "Expert opinion" section presents the analytic material prepared by the leading Russian scientists and dedicated to the main positions of the European guidelines on anticoagulant therapy in patients with atrial fibrillation.

Traditionally, our journal reviews the results of clinical studies presented at major scientific events. In this issue we publish the report on the annual Congress of the European Society of Cardiology that was held in Munich (Germany) on August 25-29, 2018.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

Rafael G. Oganov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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LEADING ARTICLE

Cardiovascular Management in Cancer Patients With Thrombocytopenia

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Abstract

Cardiovascular disease and cancer are two of the leading causes of death worldwide. Although these disease processes are separate, they share a number of common risk factors. With millions of cancer survivors, the prevalence of coronary artery disease in cancer patients will continue to increase. Chemotherapy/radiation therapies carry a risk of cardiotoxicity and accelerated atherosclerosis. Hence, management of acute coronary syndrome (ACS) in this subset of cancer patients is challenging. There are limited established management strategies to address the management of ACS in cancer patients.

Thrombocytopenia in cancer patients presenting with ACS complicates the management of ACS requiring intervention, dual antiplatelet therapy, and stent placement. Randomized trials are lacking in these patients. The complexity of managing patient with malignancy who is concurrently suffering from ACS and thrombocytopenia requires attention to management of these patients. This review article intends to highlight the pathophysiology of cancer- related thrombocytopenia and management of these patients with coronary artery disease.

Keywords: *acute coronary sy14ndrome, Cancer, Thrombocytopenia, Chemotherapy.*

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Introduction

Cardiovascular disease and cancer are two of the most common causes of mortality in the United States (1). Common risk factors for cardiovascular disease are also established predisposing factors for developing cancer including hypertension, hyperlipidemia, smoking, and family history, placing a large portion of the population at risk for these two major causes of morbidity and mortality [1]. Often overlooked are the short- and long-term effects of cancer treatment on cardiovascular disease. Cancer-related thrombocytopenia, either acute or chronic, poses a challenge in the management of coronary artery disease (CAD). Despite advances in the management of acute coronary syndromes (ACS) and chronic CAD including drug-eluting stents and dual antiplatelet therapy (DAPT), altered physiology and limited data in cancer patients lead to management dilemmas, especially with respect to thrombocytopenia. Thrombocytopenia not only increases the risk of bleeding, but also changes the hemodynamic milieu to promote a prothrombotic state due to the properties of platelets in thrombocytopenia. With the aging population and rising prevalence of cancer patients and survivors, the implications of chemotherapy and radiation therapy-induced thrombocytopenia on cardiovascular disease need to be understood. This review will discuss the pathophysiology of CAD in cancer patients with thrombocytopenia, the identification of cancer patients at risk for thrombocytopenia and CAD, and management strategies for ACS and CAD in cancer patients with thrombocytopenia.

Molecular Mechanisms of Ischemia in Cancer Patients with Thrombocytopenia

Platelets are the first responders to any acute injuries. They play a major role in pathogenesis of thrombosis and ischemic events through activation, aggregation, and degranulation. The activation sequence starts as circulating platelets come in contact with exposed collagen fibers of injured endothelium or extracellular matrix of tumor cells [2]. Once activated, degranulation of platelets releases adhesion molecules, coagulation factors, fibrinolytic factors, growth factors, and pro-inflammatory factors [2]. Factors such as thromboxane A_2, thrombin, and adenosine diphosphate recruit additional platelets and lead to formation of thrombus as surface receptors of the platelets form bonds and aggregates. Cancer cells regulate these mechanisms in a similar way by releasing prothrombotic factors like thrombin, tissue factors, and prostaglandin E_2. Hence, the risk of thrombosis in cancer patients is even greater.

Thrombocytopenia and prothrombotic states in cancer are well known. Most malignant cells disseminate hyperactive reticulated platelets [3], tissue factor, and procoagulant factors [4, 5] which regulate the formation of thrombus (Figure 1). The incidence of arterial thromboembolism is higher within the first six month of diagnosis of cancer [6]. The pathophysiologic mechanism of thrombus formation due to active malignancy is known, but the formation of thrombosis in the setting of acquired thrombocytopenia in cancer patients remains a poorly understood topic. Evidence of accumulated tissue factors within fibrin-platelet thrombi [7, 8] and activation of the extrinsic

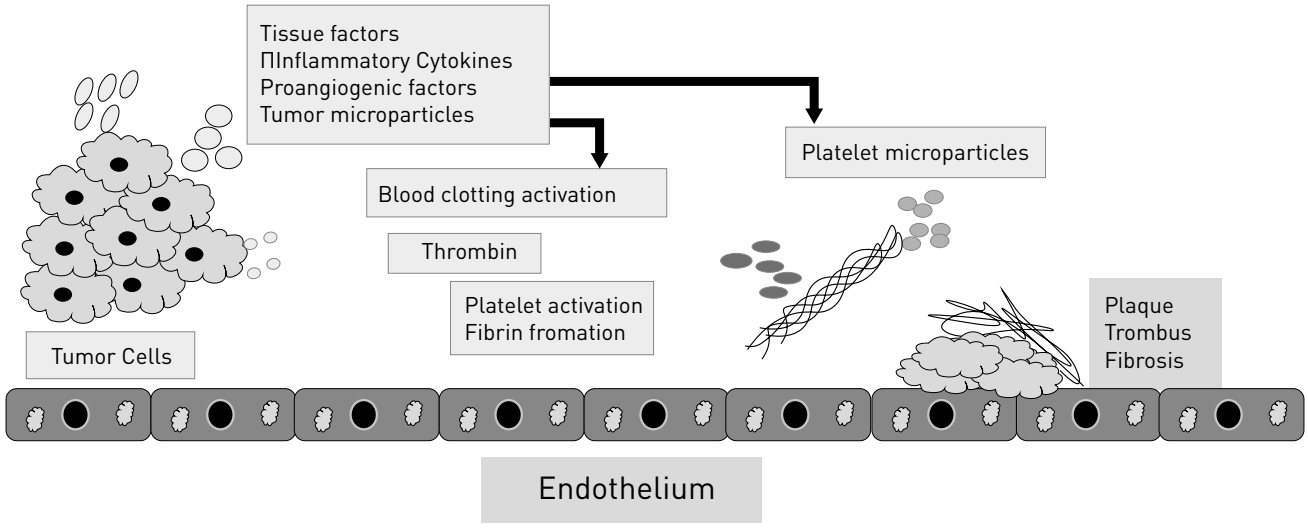

Figure 1. Tumor cells release various pro-coagulopathic particles, which enhance the extrinsic and intrinsic pathways, eventually increasing the risk of thrombus formation. This can occur both in the local vicinity and in the systemic circulation.

pathway via granules of malignant promyelocytes [8] in patients with acute promyelocytic leukemia support that severely thrombocytopenic patients are also susceptible to hypercoagulability.

Thrombocytopenia by definition is a reduced platelet count which does not protect against forming thrombus. The microvascular hemostasis and the properties of platelets are vastly affected in thrombocytopenia. It can be stated that the vulnerability of thrombus formation is due to the hypercoagulability microparticles of malignancy and the altered properties of platelets in acquired thrombocytopenia. Arterial thrombus is largely platelet rich, and hence understanding the properties of platelet in cancer state is important [9]. Chronic thrombocytopenia increases the amount of megakaryocyte production, and results in larger platelets [10]. These large platelets tend to have higher thrombotic potential and may predispose to acute cardiac events [11, 12]. In the event of a ruptured atherosclerotic plaque, these platelets are subject to high shear forces, thereby promoting adhesion and thrombus formation [13]. Furthermore, prothrombin, fibrinogen, factor V, and factor VII, all of which participate in the coagulation cascade [2], are noted to be elevated in patients with ACS and thrombocytopenia [14, 15]. Hence, platelet function rather than the absolute platelet count is a driving factor in the development of ACS in cancer patients with thrombocytopenia.

Mechanisms of Chemotherapy and Radiation-Induced Ischemic Heart Disease

Many chemotherapeutic agents have been identified in developing ischemia and arterial thrombosis. Chemotherapy alters cardiovascular infrastructure through remodeling of the microvasculature architecture by direct vascular toxicity and cellular damage, which can result in CAD, ACS, stroke, heart failure, and arrhythmias. Angiogenesis inhibitors, alkylating agents, antimetabolites, and antimicrotubules are known to cause cardiovascular toxicities through endothelial dysfunction, platelet aggregation, reduced levels of nitrous oxide, elevated levels of reactive oxygen species, and vasospasm [16].

One of the many unwanted side effects of chemotherapy is acquired thrombocytopenia which also contributes to myocardial ischemia. Thrombocytopenia predisposes patients with CAD to ischemic events within 30 days [17, 18]. Table 1 lists some of the common chemotherapeutic agents known to cause myocardial ischemia and thrombocytopenia.

Table I. **Chemotherapeutic agents associated with myocardial ischemia and thrombocytopenia**

Chemotherapeutic Agent	Uses
Cisplatin [19-21]	Squamous cell of head and neck, bladder, cervical, ovarian, testicular, mesothelioma.
Sunitinib [22, 23]	Renal cell, gastrointestinal stromal tumor, pancreas tumor
Pozapanib [24, 25]	Renal cell, soft tissue sarcoma
Nilotinib [26-28]	Chronic Myeloid Leukemia
Ponatinib [29, 30]	Chronic Myeloid Leukemia
Capecitabine [31, 32]	Colorectal, breast cancer
5-Flourouracil and Sorafenib [33, 34]	Colorectal, pancreas, gastric, breast, squamous cell cancer of head and neck

Radiation therapy is used in approximately 50% of cancer patients [35]. The site and doses of radiation are significantly linked to developing cardiac disease. For example, childhood cancer survivors who received high doses of radiation are at high risk of developing heart disease [36]. Increased cardiac mortality has been associated with left- sided breast cancer radiation as opposed to right-sided breast cancer [37, 38]. The most common manifestations of radiation-induced heart disease include accelerated atherosclerosis, and adverse myocardial remodeling. The onset of these complications is usually observed more than a decade after therapy. However, some of these changes can be noted within days of radiation exposure [39, 40]. Ionizing radiation helps in cancer eradication by inflicting cellular injury and distorting numerous molecular processes (Figure 2). The cellular membrane disruption leads to an unopposed release of various intracellular factors including procoagulants and tissue factors with often wide spread complications including progression of cholesterol plaques, inflammation, thrombocytopenia, thrombosis, and fibrosis [35].

Management of Stable CAD in Cancer Patients

The onset of CAD is multifactorial in cancer patients. In addition to the heightened risk of CAD in cancer patients' due to a systemic biochemical imbalance of hemostasis, chemotherapy and radiation therapy themselves can both cause and worsen ischemia. Vasospasm, endothelium damage, and oxidative stress in cancer patients undergoing therapy are the culprit factors of developing CAD [16]. Coronary events have been reported to occur two years prior to the time of cancer diagnosis [41] and within a few months of diagnosis [42].

The goal in treating patients with CAD and cancer is to improve survival and quality of life. Identifying

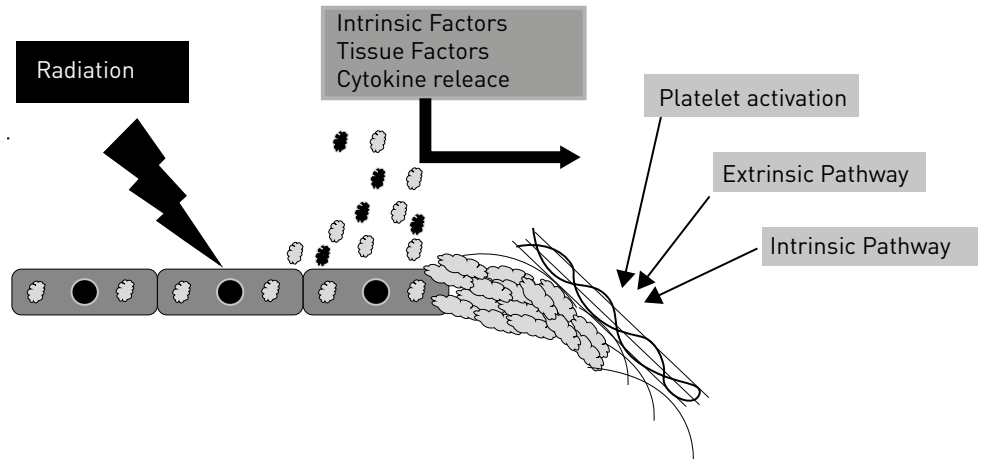

Figure 2. Radiation causes thickening of the arterial lining, eventually provoking atherosclerosis. The cellular damage by ionizing radiation also alters major biochemical pathways and releases micro-granules which have propensity to active coagulation pathways.

patients with increased risk of developing CAD is the crucial part of early detection and management of stable CAD. For example, adult survivors of childhood malignancies, breast cancer survivors are associated with late presentation of heart disease [35, 43]. These high-risk patients should be screened annually. Further screening with electrocardiography, echocardiography, or stress testing should be utilized based on expert consensus [44]. A collaborative team including a cardiologist and oncologist would provide an individualized approach in managing these patients.

In addition, other cardiovascular risk factors such as hypertension, obesity, and smoking should be identified and promptly treated. Bevacizumab, sorafenib, and sunitnib cause iatrogenic systemic hypertension [45]. Angiotensin-converting enzyme inhibitors (ACE-I) have been shown to improve overall survival in renal cell carcinoma patients being treated with sunitinib [46]. Beta blockers have been shown to improve mortality in patients receiving radiation for non-small-cell lung cancer [47]. In another retrospective study, beta blockers and aspirin improved survival of patients with myocardial infarction (MI) and cancer [48]. The treatment options for these patients are largely based on studies performed in non-cancer patients. Prophylactic cardioprotective treatment with beta-blockers, statins, and ACE-I have been recommended by several society guidelines [35, 48-54]. Randomized controlled trials studying the efficacy of using such cardioprotective regimens in cancer patients are lacking. It has also been recommended to stratify patients based on risk factors in order to initiate or continue cardio protective medication [35, 44, 55] (Figure 3).

Managing ACS in Cancer Patients with Thrombocytopenia

ACS is the result of a complex interplay between the vulnerable atherosclerotic plaque and hematopoietic system dysfunction, both of which are prevalent in oncology patients. The indication to take a non-cancer patient for early revascularization [57], and subsequent stenting is dictated by standardized, evidence-driven protocols. Malignancy- driven hypercoagulability and weakening of mucosal barriers due to chemotherapy expose vessels to an increased risk of thrombosis and bleeding [58]. The management of cancer patients in an acute setting has more limited evidence, and becomes cumbersome with concurrent thrombocytopenia which may defer potential clinical benefits of coronary intervention which requires antiplatelet therapy. Low platelet count, coagulation abnormalities, and bleeding are major roadblocks in the effective management of ACS in these patients. The conglomeration of these pathologies makes management difficult.

The benefit of reperfusion therapy for ACS is well established. Thrombolytic or percutaneous coronary intervention (PCI) both reduces the mortality and morbidity during the initial onset of symptoms [59]. There is no absolute contraindication to use thrombolytic agents in patients with ACS and thrombocytopenia. However, profound thrombocytopenia has been associated with intracranial bleeding. The American Heart Association guidelines recommend that platelet counts less than 100,000 is an absolute contraindication to administer thrombolytic in the setting of acute stroke to avoid fatal complications [60]. There is no absolute contraindication to use fibrinolytics

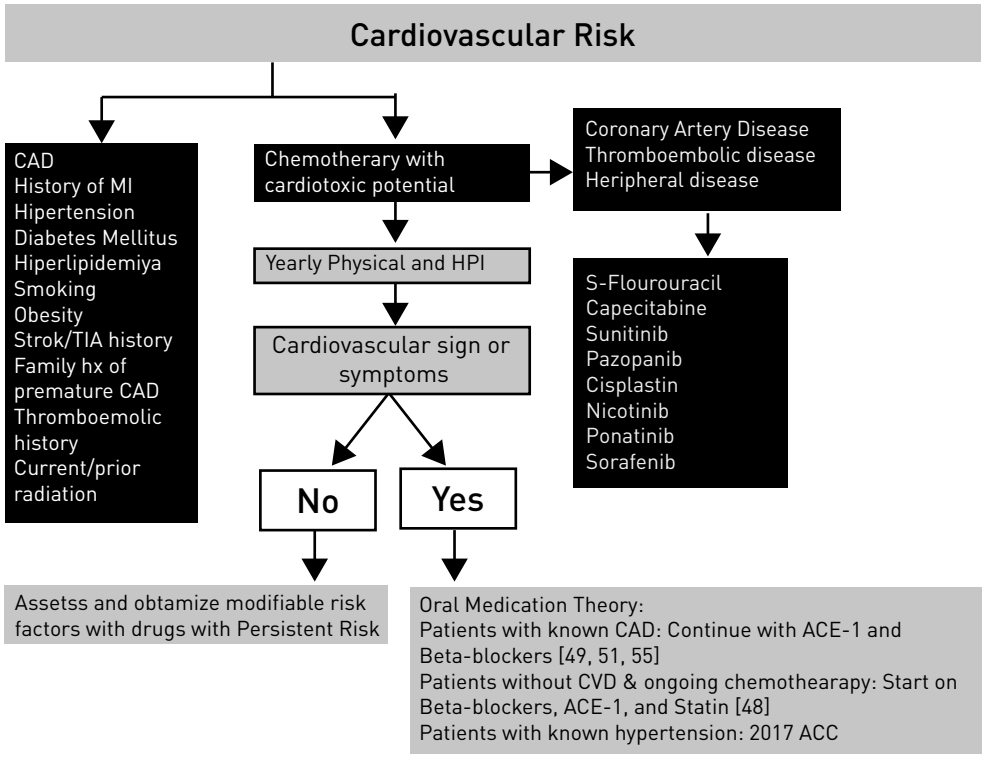

Figure 3. Patients should be risk stratified with cardiovascular risk factors. Patients with known coronary artery disease (CAD) might provide additional cardio protection by adding beta blockers or angiotensin-converting enzyme inhibitors (ACE-I) [42, 49, 53]. New onset of hypertension or established hypertension should be treated according to recent proposed hypertension guideline even though cancer as a subset group of patient population was not discussed [56]. Beta-blockers, statins, or ACE-I can be used prophylactically for patients on chemotherapy and with no cardiovascular disease (CVD) [48].

in thrombocytopenic patient for ACS. The increased risk of bleeding diathesis limits its use [59].

The role of DAPT poses another hurdle when a thrombocytopenic patient presents with ACS and requires coronary intervention. Although the overall risk of death is higher in the cancer population [61] than in the general population, cancer and non-cancer patients have no significant difference in cardiac death over the 1-year period following MI. In general, patients with leukemia and lymphoma have worse outcomes, but a potential contributor is a physician's bias of avoiding medical therapy or PCI because of the underlying comorbidities and perception of enhanced adverse effects [48]. Despite less definitive clinical pathways, patients with hematologic malignancies routinely undergo invasive cardiac procedures with acceptable outcomes [13, 62, 63], and neither leukemia nor thrombocytopenia are absolute contraindications to primary PCI. The following concerns are major dilemmas in cancer patients with ACS and thrombocytopenia.

1. Safe platelet count thresholds to carry out coronary interventions

2. Stenting in thrombocytopenia can complicate management of DAPT

3. Non-elective, cancer-related surgical interventions in the setting of DAPT

Quality versus Quantity of Platelets in Thrombocytopenia

There is no minimum platelet level that is an absolute contraindication for PCI (64). Normally, a heparin bolus of 50-70 U/kg is given during the procedure for patients with platelet counts greater than 50,000/mm^3, with additional heparin administered to maintain the activated clotting time (ACT) of about 250 seconds. A heparin dose of 30-50U/kg is administered in patients with platelet counts less than 50,000/mm^3 [13, 35]. Platelet counts as low as 40,000-50,000/mm^3 is typically sufficient to perform major interventional procedures in the absence of coagulation abnormalities [64, 65]. In patients with platelet counts <10,000/mm^3, the risks of bleeding must be balanced against the risk of not intervening [55]. Patients with platelet counts as low as 10,000/mm^3 have underwent successful cardiac interventions [13]. However, in clinical practice, most interventionists feel uncomfortable performing PCI in the setting of profound thrombocytopenia. Despite these challenges, standardized guidelines for blood transfusion for coronary inter-

ventions are lacking. The standard recommendation for prophylactic transfusion is for platelet counts less than 10,000/mm^3 in chronic thrombocytopenia and less than 20,000/mm^3 in higher risk patients [64]. One may argue in favor of transfusion when the platelet count rather than the platelet function is the concern. In these cases, it is advised to use ABO-compatible platelets as it decreases the rate of refractory platelet transfusion [66].

PCI should be the standard for oncology patients presenting with ACS irrespective of the presence of thrombocytopenia in the absence of active bleeding. Patients with malignancy, and thrombocytopenia presenting with ACS have the same constricted time for any acute coronary intervention. Thus, alternative approaches to assess the platelet function besides the platelet count may offer a better management approach. For example, modalities such as thromboelastography (TEG) can evaluate platelet and coagulation function, which can guide the need for transfusion. TEG analyzes the elastic property of whole blood and provides an assessment of hemostatic function. Transfusion based on abnormal TEG has been utilized by few cardiovascular and liver transplant teams [67, 68] and reported to have overall successful outcomes. Even though reports of TEG- guided transfusion in thrombocytopenia are limited, it may be an alternate way of assessing thrombocytopenic patients requiring cardiac interventions.

Access and Stenting

In general, cancer patients are at high risk of bleeding diathesis and are vulnerable to infection. It is important to minimize these stumbling blocks by using extra precautions in maintaining a sterile setting along with frequent catheter and sheath flushing (35). Ultrasound -guided access and use of micropuncture technique can offer to further mitigate the risk of bleeding [69-71]. A femoral access allows more flexibility during intervention, but a radial access is associated with a reduced risk of bleeding [72] and should be the preferred approach in thrombocytopenic patients [73, 74].

The onset of ACS in cancer patients is increased by chemotherapy infusion or vulnerability of platelet aggregation. Depending on the etiology, the patient may or may not require invasive intervention. Whether the coronary intervention is emergent or elective, intraprocedural evaluation of the coronary anatomy is the initial crucial step. Fractional flow reserve (FFR) has been demonstrated to be an accurate way to evaluate the functional severity of coronary lesions and to determine the next step [75]. In the absence of a culprit lesion or ischemic biomarkers, FFR may allow patients to continue on medical therapy with a favorable outcome [76]. Most cancer surgeries are not elective, and stent placement can postpone necessary interventions. Cancer therapy can complicate post stenting DAPT management. The clinical outcome of cancer patients with thrombocytopenia overlaps with numerous decision making. In non-emergent cases, noninvasive ischemic evaluation with stress tests, and assessment of myocardial structure and function with echocardiography can be helpful in assessing patients and should be undertaken prior to catheterization. Nevertheless, liberal use of FFR during the acute setting can defer stenting in patients with hemodynamically insignificant disease. The clinical outcome of medical therapy in deferred revascularization for FFR <0.8 and >0.75 had no significant difference [77]. Use of FFR can also allocate time for completing cancer therapy.

Theoretically, antineoplastic therapy can prolong the time period required for stent endothelialization [78]. Acute thrombosis within twenty minutes after stent placement has been reported in cancer patients [79]. Therefore, coronary stenting in patients with ongoing radiation not only raises the concern of interrupted endothelialization, but also increases the risk of thrombosis and may prolong the need for antiplatelet therapy. The main determinants of stent thrombosis in the early phase of implantation are stent underexpansion and stent dissection at the edges [18]. If stenting is inevitable, intravascular ultrasound (IVUS) or optical coherence tomography (OCT) should be utilized to guide stent sizing and deployment in order to avoid overlapping stenting which increases the risk of re-occlusion.

OCT can visualize abrupt thrombosis, aid adequate stent deployment, and detect malposition and stent dissection at stent edges [80], all of which are major pitfalls to avoid. OCT-guided PCI has been proven to have improved outcomes [81], and could ameliorate adverse outcomes in cancer patients. IVUS offers better plaque burden penetration [82] and can alternatively be used in patients with cancer or in those who underwent chemo-radiation as their anatomy is typically associated with greater fibrotic changes. Routine use of IVUS and OCT in every patient may result in less stent thrombosis complications in cancer patients with thrombocytopenia even if DAPT has to be stopped.

The Role of Antiplatelet Therapy

The duration of antiplatelet therapy depends on the indication of PCI versus medical management of ACS, stent generation and type, and individualized bleeding risk assessment. DAPT therapy is crucial to minimize the risk of stent thrombosis after PCI. Due to the complexity of malignancy, chemotherapy, and concurrent thrombocytopenia, randomized clinical trials evaluating the safety use of DAPT are lacking. The strategies to manage these distinct pathophysiological presentations are based on anecdotal experiences.

The choice of stents is usually guided by how long the DAPT can be safely continued. Bare- metal stents (BMS) take about four weeks to endothelialize with DAPT. Some new drug-eluting stents (DES) have been shown to endothelialize with three months of DAPT. However, cancer patients were not included in these studies [83]. Studies to determine the safety of DAPT therapies in the setting of thrombocytopenia are lacking. Therefore management of these patients needs to be individualized. A conservative approach including balloon angioplasty with a provisional BMS has been previously suggested [84, 85]. However, balloon angioplasty alone is associated with a higher risk of recurrent coronary events [86] and is less favorable in routine practice.

The shorter duration of use of DAPT with BMS is helpful for anticipated thrombocytopenia in the setting of ongoing cancer therapy. The use of DAPT in patients with thrombocytopenia has been reported in a few case reports in patients with acute myeloid leukemia [87, 88]. According to an expert clinical consensus, DAPT with aspirin and clopidogrel can be given when the platelet count is >30,000/mm^3, and aspirin alone can be given when the platelet count is >10,000/mm^3 [55]. Aspirin and clopidogrel are associated with less bleeding complications than are prasugrel and ticagrelor. . Prasugrel and ticagrelor are associated with thrombocytopenia and should routinely be avoided in these patients [35]. In the event noncardiac surgery is needed, it is advised to continue clopidogrel or aspirin or administer an intravenous short acting IIb/IIIa receptor blocker until shortly before surgery [35]. After surgery, the oral antiplatelet therapy should be restarted [78].

Aspirin as a single agent has been shown to be safe in patients with ACS and thrombocytopenia in a retrospective study [89]. Premedication with aspirin before PCI has shown a protective benefit [90], while withholding aspirin in cancer patients with ACS and thrombocytopenia has been harmful [89]. Aspirin alone does not increase the risk of bleeding [89]. Even in post coronary artery bypass graft patients with thrombocytopenia, continuing aspirin was associated with a longer vein graft patency with platelet counts of 10,000-20,000/mm3 in the absence of active bleeding [91]. Aspirin has been shown to increase the platelet count in patients with antiphospholipid syndrome -induced thrombocytopenia [92] and to decrease thrombus formation in patients with moderate thrombocytopenia [93]. This supports that the notion of platelet function rather than quality is the driving factor of hypercoagulability. A proposed management algorithm for thrombocytopenic patients with ACS is shown in Figure 4.

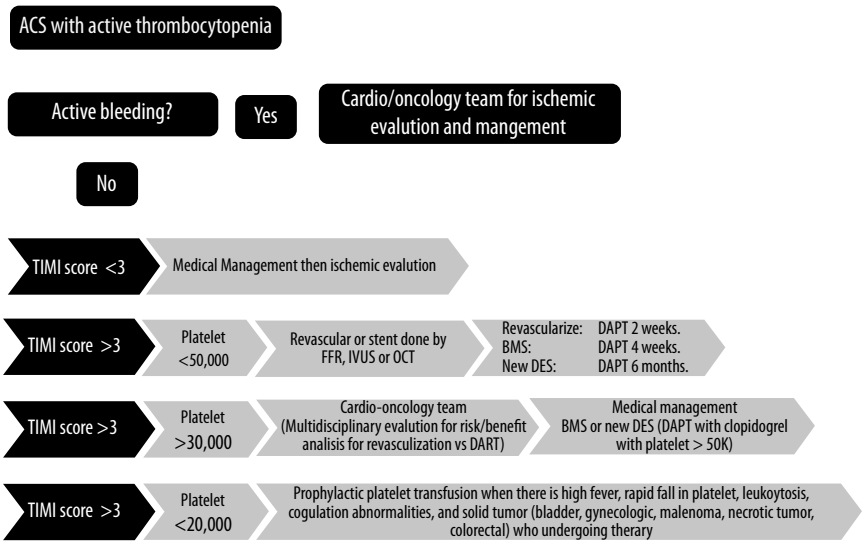

Figure 4. No minimum platelet count has been defined to be cut off criteria. A general proposal of patients with cancer and thrombocytopenia presenting with acute coronary syndrome. Each case should be individually evaluated. The proposed outline is a combination of criteria from an expert consensus [35]. ACS = acute coronary syndrome; TIMI = thrombolysis in acute myocardial infarction.; DAPT = dual antiplatelet therapy

Summary

As the growing awareness of the vascular and metabolic mechanisms of oncologic therapy continues to increase, cardio-oncology as a subspecialty requires research and educational initiatives. Many of these drugs have proven to be effective in improving cancer prognosis, but their possible cardiovascular effects have to be carefully monitored and treated. Upcoming large-scale trials including Comparative Effectiveness of 1 Month of Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy Versus a Current-Day Intensive Dual Antiplatelet Therapy in All-Comers Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and BioMatrix Family DrugEluting Stent Use (GLOBAL-LEADERS) and Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT) will give us important information on the safety of using shorter courses of DAPT.

Conflicts of interest: None declared.

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Safety of ticagrelor post fibrinolysis in STEMI patients

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Objective: *to assess the safety of ticagrelor in patients with ST-elevation myocardial infarction treated with fibrinolytic therapy.*

Materials and methods: *This unicenter, non randomized trial enrolled 200 patients (less than 75 years) diagnosed with ST-segment elevation myocardial infarction who received streptokinase from March to May 2018. One hundred Patients received ticagrelor (180-mg loading dose followed with 90 mg twice daily) while other 100 patients received clopidogrel (300-mg loading dose then 75 mg daily). Both P2Y12 inhibitors were administrated 2 hours after streptokinase, all population were naïve for any P2Y12 inhibitors pretreatment.The primary end point was thrombolysis in myocardial infarction (TIMI) major and minor bleedings through 60 days.*

Results: *At 60 days, TIMI major bleeding had occurred in 4 % of patients who received ticagrelor and in 3 % of patients who recieved clopidogrel (Odds ratio =1.3472, 95 % CI =0.293 % to 6.18 %; P =0.7014 for safety). No rates of fatal or intracranial bleeding occurred. Minor and minimal bleeding had occurred in 14 % of patients on ticagrelor and in 11 % of patients on clopidogrel (Odds ratio =1.3171; 95 % CI =0.566 % to 3.06 %; P =0.5221 for safety). After adjusting for subgroup of patients with high bleeding risk at baseline (HAS-BLED ≥3), Bleeding rates not increased in ticagrelor group (Odd ratio=1.611; 95 % CI=0.52–4.9; NNT for harm=8.4; P=0.40). RRR of bleeding rates in the clopidogrel group was only 1.25 %.*

Conclusion: *In patients younger than 75 years with ST-segment elevation myocardial infarction, delayed administration of ticagrelor for 2 hours after fibrinolytic therapy was safe and non inferior to clopidogrel for TIMI major and minor bleeding up to 60 days even in patients with high risk of bleeding (HAS-BLED score ≥3).*

Key words: *Anti platelets, Myocardial infarction, Fibrinolysis, Bleeding.*

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1. Introduction

Fibrinolytic therapy is an important reperfusion strategy in settings where primary PCI cannot be offered in a timely manner especially in developing countries outside Europe and United States of America. The largest absolute benefit is seen among patients at highest risk, including the elderly, and when treatment is offered <2h after symptom onset [1]. Intravenous streptokinase was first used in myocardial infarction (MI) in 1958. Improved survival was demonstrated in this indication in the 1980s with the publication of the first large-scale randomized GISSI–I trial [2]. Other thrombolytic agents, such as tissue plasminogen activator (t-PA), were developed and tested in a large number of clinical trials. All demonstrated a benefit in critical settings such as MI and severe PE, but they also revealed an increased bleeding risk [3]. As regard adjunctive anti platelet therapy, Clopidogrel added to aspirin reduces the risk of cardiovascular events and overall mortality in patients treated with fibrinolysis and should be added to aspirin as an adjunct to lytic therapy. Two large, randomized clinical trials have established the safety of aspirin plus clopidogrel for reducing MACE in STEMI patients treated with fibrinolysis (CLARITY and COMMIT) [4]. Only few trials looked at the safety of ticagrelor in this setting while the large randomized PLATO trial, which established ticagrelor's supremacy over clopidogrel in ACS, excluded patients treated with fibrinolysis [5]. ESC guidelines of STEMI management on 2017 recommended the switch from clopidogrel to potent P2Y12 inhibitors (ticagrelor or prasugrel) after at least 48 hours as regard the safety. This switch is passed only on expert opinions (class IIb) [6].

TREAT is the most recent randomized trial aimed to assess the non inferiority of ticagrelor to clopidogrel in STEMI. TREAT trial enrolled 3,799 patients under the age of 75 who were randomized to 180 mg ticagrelor as early as possible after the index event (within 24 hours) then followed by 90 mg twice daily for 12 months or to 300 mg of clopidogrel as early as possible, followed by 75 mg/day for 12 months. Randomization of P2Y12 inhibitors applied with a delay of 11.5 hours post fibrinolysis. For the primary outcome of TIMI major bleeding, there was no difference between study arms, with major bleeds seen in approximately 0.7% of both groups. TIMI minimal bleeding occurred more often in ticagrelor-treated patients. The authors of TREAT trial concluded that a delayed administration of ticagrelor after fibrinolytic therapy was non inferior to clopidogrel for TIMI major bleeding at 30 days,» with no benefit on efficacy outcomes.» [7].

First generation fibrinolysis (Streptokinase) has a lower bleeding risk in comparison to new generations (t-PA or TNK). Peak activity of streptokinase is found in the blood about 20 minutes after dosing. Elimination kinetics of streptokinase follows a biphasic course. A small proportion of the dose is bound to anti-streptokinase antibodies and metabolized with a half-life of 18 minutes while most of it forms a streptokinase-plasminogen activator complex and is bio transformed with a half-life of about 80 minutes [8]. Regarding these pharmacokinetic data, the bleeding risk of streptokinase is declined after 2 hours of administration. We aimed in this trial to administer the potent P2Y12 inhibitor (Ticagrelor) just after 2 hours of streptokinase bolus intake (1.500.000 U).

2. Patients and methods

2.1. Study population

This single-center, prospective, non randomized trial performed from March 2018 to May 2018. Inclusion criteria were STEMI patients under 75 years who treated with streptokinase as a thrombolytic therapy. Exclusion criteria were previous ACS, PCI or CABG, previous pre treatment with P2Y12 inhibitors or OAC.

2.2. Study protocol

Designed as a safety and non inferiority trial to estimate both major and minor TIMI bleeding risks of ticagrelor to clopidogrel as an adjunctive therapy to fibrinolysis.

Sample size of 200 patients divided equally into two groups, after receiving fibrinolytic therapy (streptokinase standard dose 1.500.00 U) within 3 hours of diagnosed STEMI attack.

Group 1 (100 patients): received ticagrelor (180-mg loading dose 2 hours after streptokinase followed with dose 90 mg twice daily).

Group 2 (100 patients): received clopidogrel (300-mg loading 2 hours after streptokinase followed with dose 75 mg once daily).

2.3. Methods

For all patients full history, clinical examination, 12 leads electrocardiogram, trans thoracic echocardiography, laboratory investigations in form of cardiac troponins, serum creatinine, liver function test, complete CBC, HbA1C, coagulation profile including INR ratio were done to assess bleeding risks.

HAS-BLED risk score was used for bleeding risk assessment at baseline, a calculated HAS-BLED score is between 0 and 9 and based on eight parameters with a weighted value of 0–2. HAS-BLED stands for Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly >65 years, Drugs or alcohol [9]. Patients in both groups had been classified into low risk of bleeding if have score ⩽2 and classified into high risk of bleeding if have score ⩾3.

2.4. Study endpoints and definitions

The study end points were composite of major or minor TIMI clinically significant bleeding:

Major defined as any intracranial bleeding, any clinically overt signs of hemorrhage associated with a drop in hemoglobin of ⩾5 g/dL or a ⩾15 % absolute decrease in haematocrit, any fatal bleeding (bleeding that directly results in death within 7 days).

Minor defined as any clinically overt bleeding, resulting in hemoglobin drop of 3 to <5 g/dl or ⩾10 % decrease in haematocrit [10].

2.5. Statistical analysis

The association between variables and treatment groups was investigated by chi-square or Fisher exact tests. Parametric unpaired Z score test was applied to evaluate differences for continuous variables between both groups. The association between type of treatment and clinical endpoints was expressed as the odds ratio (OR), and the 95 % confidence interval (CI) also was reported. Relative risk reduction (RRR) analysis was applied to detect the valuable reduction of bleeding outcomes between two groups. A p value less than 0.05 were considered significant (2-sided). All analyses were carried out using Stata 12 software (StataCorp LP, College Station, Texas).

3. Results

3.1. Study population

Demographic, clinical and bleeding risk stratification variables are presented in (Table 1). There were no significant differences between the two groups regarding age, gender, diabetes mellitus (DM), hypertension; previous bleeding or HAS-BLED score were equivalent in both groups.

3.2. TIMI major or minor bleeding rates

The endpoint of composite major and minor TIMI bleeding occurred in 18 % of the ticagrelor group (Group 1) and 14 % in the Group 2, with (odd ratio of 1.348; 95 % CI of harm = –6.29–14.25; NNT of harm = 25;P= 0.441 for safety). Isolated Major or minor bleeding occurred more in ticagrelor-treated patients with non significant differences (P=0.7 & 0.5 respectively). (Table 2 & Figure 1).

Table 1. **Demographic, clinical and bleeding risk stratification variables**

Variable	Group I 100 p	Group II 100 p	P value
Clinical variables			
Age	65±2	64±4	0.065
Female Gender	40 %	43 %	0.66
D.M	62 %	59 %	0.6651
HTN	49 %	55 %	0.396
Previous bleeding	11	9	0.638
HAS-BLED risk score			
Abnormal renal function	4	6	0.51
Abnormal liver function	5	6	0.75
Previous stroke	3	2	0.65
Labile INR	3	1	0.31
Elderly > 65 years	40	38	0.772
NSAID intake	50	40	0.156
Alcohol intake	-	1	-
Low risk of bleeding HAS-BLED <2	89	87	0.664
High risk of bleeding HAS-BLED >3	11	13	0.66
Adjunctive anticoagulants			
Un fractionated heparin	21	30	0.145
Low molecular weight heparin	79	70	0.143

Table 2. **Bleeding outcomes in study population**

Variable	Group I	Group II	Odd ratio	95% CI	RRR	NNT for harm	P value
Major TIMI bleeding	4%	3%	1.3472	0.29–6.18	1.333	100	0.7014
Minor TIMI bleeding	14%	11%	1.3171	0.56–3.06	1.272	33.3	0.5221
Total TIMI bleeding	18%	14%	1.3484	–6.29–14.25	1.285	25	0.441

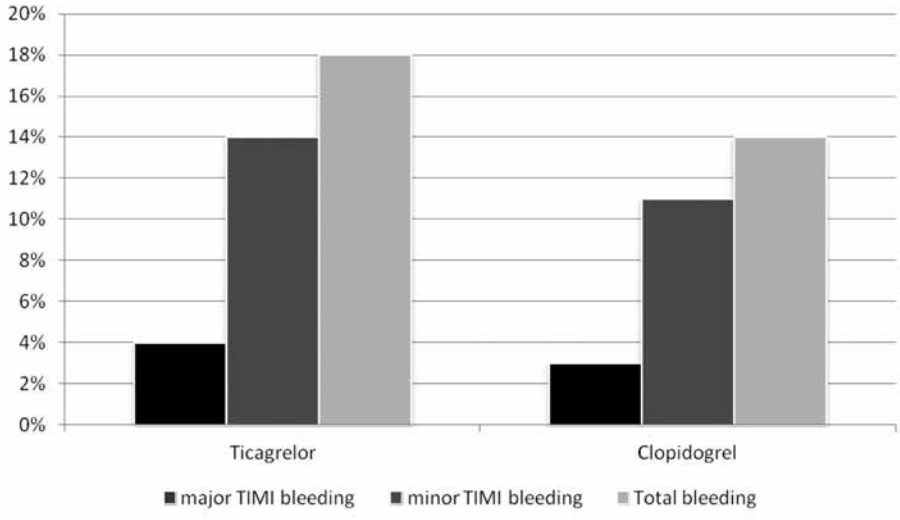

Figure 1. Bleeding outcomes in study population

3.3. Bleeding rates in high risk patients with HAS-BLED score ≥3

After adjusting for subgroup of patients with high bleeding risk at baseline (HAS-BLED ≥3), Total TIMI bleeding rates remained similar in both groups (Odd ratio=1.611; 95% CI=0.52–4.9; NNT for harm=8.4; P=0.40). The relative risk reduction (RRR) of bleeding rates in the clopidogrel group was only 1.25%. (Table 3)

4. Discussion

Ticagrelor is a novel reversible platelet inhibitor that is notable for its superior clinical efficacy and safety [11]. The efficacy and safety of ticagrelor in STEMI patients who treated with fibrinolysis remained unclear. In this study, we aimed to assess the short term safety of ticagrelor in this situation. ESC guidelines of STEMI management on 2017 recommended the switch from clopidogrel to ticagrelor after 48 hours as a safety time passed on expert opinions (class IIb) [6].

In this research, the incidence of major TIMI bleeding of ticagrelor compared to clopidogrel was nearly identical (odds ratio =1.3472, 95% CI =0.293% to 6.18%; P =0.7014 for safety). These results were in accordance with the conclusions drawn in TREAT study; TIMI major bleeding had occurred in 14 of 1913 patients (0.73%) receiving ticagrelor and in 13 of 1886 patients (0.69%) receiving clopidogrel (absolute difference, 0.04%; 95% CI, –0.49% to 0.58%; P <.001 for non inferiority). In this research, no increase of incidence of minor TIMI bleeding of ticagrelor compared to clopidogrel (odds ratio =1.3171; 95% CI =0.566% to 3.06%; P =0.5221 for safety). In TREAT, Minor and minimal bleeding were more common with ticagrelor than with clopidogrel (Table 2).

After adjusting for subgroup of patients with high bleeding risk at baseline (HAS-BLED ≥3), Total TIMI bleeding rates remained similar in both groups (Odd ratio=1.611; 95% CI=0.52–4.9; NNT for harm=8.4; P=0.40). The relative risk reduction (RRR) of bleeding rates in the clopidogrel group was only 1.25% (Table 3).

Table 3. **Bleeding rates in high risk patients with HAS-BLED score ≥3**

Variable	High bleeding risk patients in Group I (11 patient)	High bleeding risk patients in Group II (13 patient)	Odd ratio	95% CI	RRR	NNT for harm	P value
Major TIMI bleeding	4/11	2/13	3.14	0.44–21.95	2	7.5	0.248
Minor TIMI bleeding	11/11	9/13	1.44	0.43–4.75	1.22	11	0.545
Total TIMI bleeding	15/11	11/13	1.611	0.52–4.92	1.25	8.4	0.40

These results confirm that ticagrelor as a potent antiplatelet is same as clopidogrel as regards the safety. In TREAT trial, the main concern was for the bit longer delay with a median of 11.4 hours between fibrinolysis and antiplatelet administration [7].

In contrast to TREAT, in this research the safety time between ticagrelor and streptokinase was reduced for only 2 hours apart. In clinical practice early adjunctive DAPT therapy in patients with STEMI is associated with a significant reduction of in-hospital MACCE regardless of the initial reperfusion strategy [12]. Further trials with a bit shorter delays, are still recommended.

The superiority of this research as regard TREAT trial could be detected in the following: The safety of ticagrelor was documented a 30 days more than TREAT. Safety outcome observed with only 2 hours apart between ticagrelor and fibrinolysis while in TREAT, 11.4 hours was needed to achieve the safety outcomes. The inferiority of this research as regard TREAT trial, that efficacy outcome was not considered as an endpoint. Meanwhile, TREAT showed no difference as regard efficacy. The small sample size is a major limitation in this research and could affect the outcome results.

Moreover, many key questions remain unanswered, what would happen in patients who received fibrinolysis and ticagrelor at the same time. Another concern is for elderly patients > 75 years, who were excluded from this research and from TREAT, and who would be particularly susceptible to bleeding even if they were started on ticagrelor 2 hours after fibrinolytics.

Conclusion

Among patients <75 years of age who were treated with first generation fibrinolysis (streptokinase) for STEMI, ticagrelor after only 2 hours from streptokinase administration was safe and non inferior to clopidogrel. There was no excess of major bleeding, fatal bleeding, or intracranial bleeding with ticagrelor vs. clopidogrel. Ticagrelor could be the first treatment option in patients who are considered hypo responders to clopidogrel or had allergy. Unless future trials show otherwise, ticagrelor is safe 2 hours after fibrinolysis for STEMI patients.

Conflicts of interest: None declared.

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Blood pressure circadian rhythm abnormalities in patients with chronic kidney disease, stage 5

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Objective. *To detect clinical and laboratory characteristics of the course of arterial hypertension in patients with chronic kidney disease, 5 stage, receiving maintenance hemodialysis.*

Materials and methods. This study included 248 patients on maintenance hemodialysis therapy. All patients underwent 24h blood pressure monitoring (24h-ABPM) for 23,2±0,6h in order to detect abnormalities of blood pressure (BP) circadian rhythms and their relationship with metabolic parameters. Statistical analysis was performed using StatPlus 2009 software.

Results. *We found that a longer dialysis history was associated with a bigger number of patients with arterial hypotension rather than arterial hypertension (p<0,001). Daytime 24h-ABPM parameters correlated with office values of systolic BP (SBP) and diastolic BP (DBP) before hemodialysis: rSBP=0,52, p<0,01 and rDBP=0,65, p<0,01; during the procedure: rSBP=0,50, p<0,01 and rDBP=0,66, p<0,01, and after the procedure: rSBP=0,56, p<0,01 and rDBP=0,54, p<0,01. Night-peaker type of circadian rhythm was found in 34 patients (68%), whereas night levels of DBP were elevated in 22 (44%) patients. There were also patients with an insufficient decrease of nocturnal BP (non-dipper): 12 persons (24%) with corresponding SBP values and 16 (32%) with corresponding DBP values. Correlation analysis revealed the relationship between the morning SBP and DBP elevation value with urea levels (r=-0,77; p<0,001 and r=-0,87; p<0,001, respectively), potassium (r=-0,8; p<0,001 and r=-0,8; p<0,001, respectively), sodium (r=0,74; p<0,001 and r=-0,69; p<0,001, respectively), and phosphorus (r=-0,7; p<0,001 and r=-0,78;*

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p<0,001, respectively). There was also found a correlation between post-dialysis pulse pressure and the level of parathyroid hormone (rs=0,78; p<0,001), phosphorus (r=0,63; p<0,001), and calcium (r=0,57; p<0,001).

Conclusion. *Thus, long-term duration of dialysis is associated with an increase in the number of patients with arterial hypotension and a decrease in the number of patients with arterial hypertension. The majority of patients with AH had BP circadian rhythm abnormalities of non-dipper and night-peaker types. 24h-ABPM parameters correlate with electrolyte balance impairments (potassium, sodium, and phosphorus concentrations) and nitrogen metabolism (urea levels). Increased pulse pressure is associated with hypophosphatemia, hypercalcemia and elevated level of parathyroid hormone.*

Keywords: *arterial hypertension, 24h blood pressure monitoring, chronic kidney disease stage 5.*

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Cardiovascular diseases (CVD) represent the leading mortality cause in patients on maintenance hemodialysis (HD) [1, 2, 3, 4]. Arterial hypertension (AH) is a significant risk factor of cardiovascular complications in dialysis patients leading to disability and death, and, thus, determines the prognosis of the disease, as well as life duration and quality of life [5, 6, 7, 8]. In the dialysis population, hypertension is diagnosed in 55-88% of patients. According to the 2016 register, the percentage of HD patients with hypertension remains steadily high (61.1%) in Russia, in comparison to the previous years [9, 10].

Until recently, the question of the necessity and significance of 24-hour ambulatory blood pressure monitoring (ABPM) for patients on HD was debatable, since such patients on HD treatment showed a high correlation between BP values obtained during dialysis and blood pressure monitoring. The ABPM results were comparable to the values of office BP. The study of Ekart R. et al., conducted in 2009, showed that only blood pressure values obtained during the 24- or 48-hour ABPM were associated with the thickness of the blood vessels intima. In addition, a single measurement of "office" blood pressure in dialysis patients can's demonstrate the BP influence on the prognosis of the disease [11]. At the same time, Russian and foreign authors note a characteristic feature of hypertension in dialysis patients (on 85%) which is no decrease or a slight decrease of blood pressure (mainly nocturnal DBP). Since blood pressure is usually measured during the day, this can lead to an erroneous idea of good blood pressure control.

There is a correlation between the absence of nocturnal decrease in BP and the severity of damage to target organs of the cardiovascular system. Previous studies have shown that an increase in nocturnal blood pressure by more than 30% was as an independent factor of the left ventricular hypertrophy onset and progression. At the same time, left ventricular hypertrophy may be associated with an increase in total peripheral resistance, which, in turn, in patients on HD, is due to an increased vascular wall stiffness and an increased return wave [12, 13]. The simplest clinical method which can reflect arterial stiffness is the pulse pressure (PP) calculation.

Thus, ABPM in dialysis patients represents a necessary diagnostic method which determines the further management of the patient.

Objective of the study: to identify clinical and laboratory features of AH in patients with chronic kidney disease (CKD) on the 5th dialysis stage.

Materials and methods

The study included 248 patients with CKD stage 5, M / F = 129/119, aged from 18 to 61 years, who were receiving the HD treatment in the hemodialysis units of the Udmurt Republic (Izhevsk, Glazov, Votkinsk, Mozhgi, Sarapul). The dialysis was performed using devices 4008S ("Fresenius", Germany) and Dialog + (B. Braun, Germany) 3 times per week for 4–4.5 hours via polysulfone dialyzers. The Kt / V adequacy index for urea was higher than 1.2 and was 1.43 ± 0.09.

In regard to the blood pressure level, all patients were divided into three groups. The first group consisted of 173 patients with elevated BP. This group included 120 patients with grade-I hypertension, 42 patients with grade-II hypertension and 11 patients with III-grade hypertension, according to the Russian Society of Cardiology (RSC) guidelines (2004, 2010) and ESH/ESC guidelines (2013). Patients with differ-

Table 1. **Distribution of patients with different BP level depending on their dialysis history**

Dialysis history	Normal BP N=28 patients (%)	AH (%) N=173 patients (%)	Arterial hypotension N=47 patients (%)	p
Up to 1 year	8(28.6)	54(31.2)	7(14.9)	$p_{1-2}>0.05$ $p_{2-3}<0.05$ $p_{1-3}>0.05$
2-5 years	5(17.8)	69(39.9)	11(23.4)	$p_{1-2}<0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$
6-10 years	7(25)	29(16.8)	11(23.4)	$p_{1-2}>0.05$ $p_{2-3}>0.05$ $p_{1-3}>0.05$
More than 11 years	8(28.6)	21(8.5)	18(38.3)	$p_{1-2}>0.05$ $p_{2-3}<0.001$ $p_{1-3}>0.05$

Note: p – significance of difference between groups according to Pearson criterion χ^2

ent hypertension grades were comparable on age and sex and had AH history of 13,4±1,1years.

The second and the third group consisted of 28 and 47 patients with normal and low BP respectively. The groups were comparable on age and sex.

Patients' examination program included general and special methods. 50 patients underwent blood pressure monitoring during 23,2±0,6 hours (using the IECG-DP-NS-01 device, 2008) in order to reveal circadian rhythm of BP abnormalities and their relationship with metabolic parameters. The correlation between the 24h-ABPM values and biochemical parameters according to diagnostic standards for patients on hemodialysis, such as, creatinine 780.45 + 199.9 μmol /L), urea (29.4 + 6.9 mmol /L), potassium (5.33 + 0.47 mmol /L), sodium (137.7 + 2.1 mmol /L), calcium (2.52 + 0.5 mmol /L), phosphorus (2.1 + 0.4 mmol /L), alkaline phosphatase (311.7+ 155.2 U /L), total cholesterol (5,1 + 1,2 mmol /L), parathyroid hormone (PTH) 526 [252; 895] pg /L was studied. Local Ethics Committee permission was obtained before the start of the study.

Statistical analysis of obtained results was carried out using the BioStat (2009, version 4.03.) and Microsoft Excel 2010 application programs. Statistical analysis was performed using parametric and non-parametric statistical methods. The data were described as M ± m. The reliability of the research results was confirmed by Student's criterion (t) value calculation. The χ^2 criterion was used to reveal the differences between groups according to their qualitative characteristics. Pearson (r) and Spearman (rs) correlation analysis was also applied.

Results

In our study, the number of patients with dialysis history of up to one year was 54 for the group with elevated BP (31.2% of all patients with elevated pressure), 8 for those with normal BP (28.6%), 7 – with low BP (14.9%; see Table 1). Among patients with the dialysis history of 2-5 years, there were mostly individuals with elevated blood pressure – 69 persons (39.9%; p <0.01). In the group with dialysis history of 6-10 years, the distribution of patients with different levels of blood pressure was statistically unreliable. In the group with dialysis history of more than 11 years, low blood pressure was observed in 18 (38.3%) patients, normal BP – in 8 patients (28.6%), elevated BP – in 21 (8.5%) patients (p <0.001). Therefore, a longer dialysis history leads to a decrease in the number of individuals with hypertension and an increase in the number of those with hypotension (Table 2).

Patients with AH underwent 24h-ABPM (Table 3). It was found that average integral indicators of SBP

Table 2. **"Office" BP values in patients on maintenance HD**

Parameter, mm Hg	**BP, mm Hg. (N=248)**
SBP in the beginning of the HD procedure (M±m).	135.3±1.5
DBP in the beginning of the HD procedure (M±m).	81.8±0.8
SBP in the end of the HD procedure (M±m)	133.7±1.9
DBP in the end of the HD procedure (M±m)	80.5±0.9

Table 3. **24h BP monitoring parameters in patients with arterial hypertension**

Parameter	SBP (N=50)	DBP (N=50)
Average integral value for 24 hours, mm Hg.	144.2±5.8	94.2±3.8
Average integral diurnal value, mm Hg.	143.7±6.4	93.9±3.9
Average integral nocturnal value, mm Hg.	145.9±5.5	95.2±4.3
Hypertonic time index	70.8±18.6	74.4±16.3
Magnitude of Morning Surge in BP (MSBP), mm Hg.	4.3±6.5	3.5±4.7
RoR (morning rate of rise), mm Hg/hour	1.8±1.9	1.1±1.7
Nocturnal BP decrease rate	-2.2±2.4	-0.14±2.6

and DBP exceeded the permissible values and were, respectively, 144.2 ± 5.8 mm Hg and 94.2 ± 3.8 mm Hg for 24 hours, 143.7 ± 6,4mm Hg and 93.9 ± 3.9 mm Hg for the day hours, 145,9±5,5 mm Hg and 95,2±4,3 mm Hg for the night hours. As shown in the table, the SBP and DBP time index is significantly increased, which indicates not a transient, but a stable character of hypertension. Diurnal ABPM values correlated with the "office" SBP and DBP values before the hemodialysis procedure : 136.8 ± 5.8 mm Hg and 82.5 ± 3.9 mm Hg (r_{SBP} = 0.52, p <0.01 and r_{DBP} = 0.65, p <0.01), during the hemodialysis procedure: 133.8 ± 5.7 m Hg and 84.2 ± 3.5 mm Hg (r_{SBP} = 0.50, p <0.01 and r_{DBP} = 0.66, p <0.01), after the hemodialysis procedure: 134.8 ± 7.9 mm Hg and 82.9 ± 3.9 mm Hg (r_{SBP} = 0.56, p <0.01 and r_{DBP} = 0.54, p <0.01).

It is well-known the BP undergoes significant fluctuations in the course of a day; these daily fluctuations reflect the circadian rhythm which is characterized by a BP decrease during the night sleep and a rapid increase at the moment of awakening or immediately before it. Night-peaker circadian rhythm, characterized by paradoxical nocturnal hypertension, i.e. a distinct BP elevation at night, occurred in 34 (68%) patients; DBP elevation was observed in 22 (44%) patients (Figure 1). The morning BP elevation value was negative in 16 (32%) patients for SBP and 22 (44%) patients for DBP: therefore, in these cases, there is a decrease and not an increase in the morning BP. There were also individuals with an insufficient decrease in nocturnal BP (non-dipper): 12 (24%) persons for SBP, and 16 (32%) persons for DBP. Normal diurnal rhythm (Dipper) was observed in 4 (8%) patients for SBP and 12 (24%) patients for DBP. There was no patient with an excessive decrease in nocturnal BP in our study.

In recent years, increasing attention is being paid to heart rate (HR), which is considered an independent risk factor for cardiovascular complications. It is important to note that some authors tend to consider tachycardia an indicator of an increase in the activity of the autonomic nervous system. Patients included in this study had the heart rate of 76 [74,8; 81,8] beats/min during the 24h-ABPM. This parameter exceeded the reference values in 12 patients (24%). Kerdo vegetative index corresponded to the prevalence of parasympathetic tone in 44 patients (88%), of sympathetic tone in 6 patients (12%), and it's average value was –20.2 ± 5.5.

Also, various authors note the role of pulse pressure in the development of cardiovascular events [14]. When measuring "office" blood pressure, the pulse pressure at the beginning and in the end of the hemodialysis procedure was 53.5 ± 1.0 mm Hg and 53.3 ± 1.2 mm Hg, respectively (p> 0.05). The distribution of the pulse pressure level was as follows: 127 (51.2%) patients had elevated values, 88 (35.5%) patients had normal values, and 33 (13.3%) patients had borderline values. The correlation analysis revealed a relationship between the pulse pressure at the end of the hemodialysis procedure and the level of PTH (rs = 0.78; p <0.001), phosphorus (r = 0.63; p <0.001) and calcium (r = 0.57; p <0.001).

Via correlation analysis, there was also found a relationship between the SBP and DBP morning elevation magnitude and the level of urea (r = -0.77; p <0.001 and r = –0.87; p <0.001, respectively), potassium (r = –0.8; p <0.001 and r = –0.8; p <0.001, re-

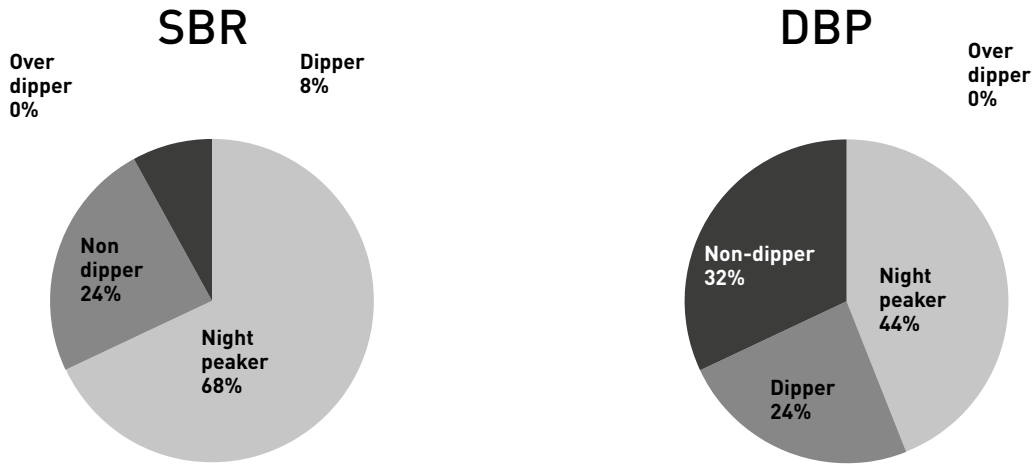

Figure 1. BP circadian rhythm features in patients with AH

spectively), sodium (r = 0.74; p <0.001 and r = 0.69; p <0.001, respectively) and phosphorus (r = –0, 7; p <0.001 and r = –0.78; p <0.001, respectively). These correlations indicate that the higher the concentration of metabolites (urea and creatinine) and ions (potassium, sodium, phosphorus) in the blood is, the greater is the likelihood of nocturnal hypertension. In our study, the morning BP elevation magnitude was the only 24h-ABPM parameter to be correlated with biochemical parameters (Table 4).

Table 4. **Correlation of biochemical parameters and the magnitude of morning BP surge**

Parameter	magnitude of morning SBP surge (r)	magnitude of morning DBP surge (r)
Urea	-0,77**	-0,87**
Potassium	-0,8**	-0,8**
Phosphorus	-0,7**	-0,78**
Sodium	0,74**	0,69**

Note: correlation coefficient reliability - **p<0,001;

Discussion

The results of our research show that BP values depend on the duration of the hemodialysis therapy history. With a longer dialysis history, an increase in hypotonic patients number and the decrease in the hypertonic patients number can be observed (p<0,001). It may be associated with the heart failure progression, when there is a decrease in the ejection fraction, and, consequently, a BP decrease [15]. Myocardial remodeling develops under the influence of various urotoxins (FGF-23, urea, potassium, PTH, renin, etc.) and chronic mechanical overload of the myocardium [16, 17, 18].

More than a half of patients (51.2%) had an elevated level of pulse BP. Some authors associate the pulse pressure increase with an increase of the main arteries rigidity [14]. We found a correlation between pulse pressure and the level of PTH, phosphorus and calcium (p <0.001). It is known that the CKD and secondary hyperparathyroidism progression leads to medial sclerosis, or Mönckeberg's arteriosclerosis, which is characterized by sclerotic lesion of the arterial media of elastic or elastic-muscular arteries and manifests as the media necrosis, sclerosis or calcinosis. [19].

Therefore, the severity of calcium-phosphorus metabolic disturbances has a direct impact on the CVD prognosis in this cohort of patients. A review of seven studies (EWPHE, HEP, MRC1, MRC2, SHEP, Syst-Eur and STOP) showed that PP was an independent risk factor of death from cardiovascular disease [20]. According to Klassen P.S. (2002) and USRDS Waves 3 and 4 Study (2010) in patients with HD, the risk of death increased by more than 10% with an increase in post-dialysis PP by 10 mm Hg. [21, 22, 23]. Thus, the pulse pressure control and the effective correction of calcium-phosphorus metabolism represent significant prognostic factors.

In November 2017, the American College of Cadiology and the American Heart Association presented new guidelines for hypertension, where new approaches to patient management and diagnosis were established. Thus, the target level of blood pressure, regardless of comorbid pathology, was established to be less than 130/80 [24]. Russian guidelines, though, regard hypertension today in the same way as the guidelines of the European Society of Cardiology and the European Society of Hypertension (2013) [25] do: target blood pressure for all patients with hypertension, regardless of risk, should be less than 140/90 mm Hg, and exactly 130–135 / 80–85 mm Hg [26]. At the same time, a large study showed that if the post-dialysis SBP is less than 120 mm Hg, there is an increase in the incidence of cardiovascular events in patients on HD [27]. Another study was conducted to check this data: it included 649 hemodialysis patients and showed that that hypertension, on the contrary, was associated with better survival, while patients with hypotension had a higher mortality rate [28]. It is also worth noting that hypotension episodes during dialysis often provoke fatal arrhythmias, which is the main cause of sudden death in dialysis patients.

The first guidelines on the target level of blood pressure in the dialysis cohort of patients appeared in Japan (2014), where target BP values were defined as from 130 to 159 mm Hg for SBP and from 70 to 89 mm Hg for DBP. [29]. Thus, both hypertension and hypotension after the HD session are associated with an increased risk of death.

The results obtained by us show that the "office" BP values are highly correlated with diurnal 24h-ABPM values, but do not reflect nocturnal blood pressure, and, therefore, do not assess the degree of hypertension in dialysis patients. The overwhelming majority of patients with hypertension had a circadian rhythm disorder of the non-dipper type, which is characterized by an insufficient nocturnal decrease of BP, and the night-peaker type, characterized by paradoxical nocturnal hypertension. According to Agarwal R. Pro (2015), 24h-ABPM was the best way to predict mortality risks in comparison to the "office" and "home" BP measurement[30]. But for today the 24h-ABPM is not widely used due to low availability of equipment and

certain practical difficulties for the patient. Therefore, it is necessary to include the 24-hours blood pressure monitoring in the medical care standards for dialysis patients, and, in prospect, the 24-hours monitoring of blood pressure via radial artery applanation tonometry.

Conclusion

Arterial hypertension occurs in 69.8% of patients on maintenance hemodialysis in the Udmurt Republic. With an increase of the dialysis history, there can be observed a decrease in the number of patients with arterial hypertension and an increase in the number of patients with arterial hypotension. Most patients with hypertension have circadian rhythm abnormalities of non-dipper and night-peaker types.

We also revealed a relationship between 24h-ABPM values and ionic balance changes (potassium, sodium, phosphorus), as well as nitrogen metabolism indicators (urea level). The increase in pulse pressure was associated with hyperphosphatemia, hypercalcemia and an increased PTH level. 24h-BPM is indispensable for an adequate hypertension diagnostics and, together with antihypertensive therapy, for an effective correction of calcium-phosphorus metabolism.

Conflict of interest: None declared

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Dynamics of risk factors and cardiovascular diseases: analytical review of international and Russian data for 2017

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This review article discusses the data on lifespan and dynamics of cardiovascular diseases (CVD) in Russian working age population in 2017. It provides information on specialized high-tech healthcare methods for patients with CVD. Improvement of screening and risk factors detection is noted, and it contributes to improvement of CVD primary prevention. The second part of the article reviews analytic material on main risk factors in working age men and women in Russia comparing with the other countries, taken from the European Society of Cardiology (ESC) Atlas of Cardiology. Russia is in the top ten list of countries with high prevalence of hypertension, smoking, obesity and sedentary lifestyle among 56 countries-members of the ESC.

Keywords: *risk factors, prevalence, cardiovascular diseases, ESC Atlas of cardiology&*

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According to the Ministry of Health of the Russian Federation, 2017 will be remembered as a year of cautious optimism with positive dynamics of such important indicators as life expectancy and reduction of some socially significant diseases, including cardiovascular complications. This year has been highlighted with improved availability of medicine, implementation of high technologies and prevention of chronic non-infectious diseases (CNID).

In 2017, the average life expectancy of Russians reached a national historical maximum of 72.6 years. Since 2005, it has increased by 8.6 years in men and by

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5 years in women. Total mortality fell by more than 2 percent, to 12.5 cases per 1000, thus meaning that 35 000 more lives had been saved in 2017. For 11 months of 2018 46 400 more lives have been saved comparing with 2017. The frequency of all mortality causes has decreased. The result of tuberculosis control is particularly impressive. This year mortality rate has decreased by 17 % to 6.3 per 1000 persons [1].

A system of emergency specialized medical care has been created in six years. It includes 593 vascular centres focused on intensive cardiological and neurological care. In addition, more than 1500 trauma centres have been commissioned. As a result, the number of patients with stroke who received modern thrombolytic therapy within the first 4.5 hours became 30 times bigger, and the number of patients who received neurosurgical treatment increased sevenfold. The volume of coronary artery stenting operations has tripled. It resulted in 54 % and 13.5 % fall of mortality rate due to stroke and myocardial infarction, respectively, whereas death from road accidents decreased by 27 %.

CNID prevention is the absolute priority of the Russian healthcare system. An extensive campaign against tobacco and alcohol consumption is ongoing, people are more involved into various sports, and vaccination has expanded within national immunization schedule.

This year 18 million adults and 22 million children received free health screening. Thanks to effective oncological screening, 55 % of cancer cases are diagnosed at stages I–II. Such risk factors like arterial hypertension and hypercholesterolemia are better controlled, and it has also improved the situation with heart disease [1].

WHO estimates that in 2016 Russia became one of three global leaders of effective control of non-infectious diseases [2].

Medical care accessibility is one of the state priorities in the field of social policy. This concerns primarily the regions of Russia. In collaboration with regional authorities it was possible to stop tremendous extinction of rural health units and outpatient clinics, and by now their number has reached 50 thousand. 400 new medical offices were opened in 2017. «Mobile» diagnostics is becoming habitual in the countryside, and 55 diagnostic car units are equipped for this purpose. Thanks to the «Zemsky Doctor» program, more than 26 thousand medical doctors started to work in the countryside. In 2018 this program was extended to towns with population of less than 50 thousand people. In 2015 the time-limits for waiting for different types of medical care have been established depending on their urgency. New requirements of outpatient centres' and hospitals' placement have been approved depending on population size and distance to the nearest medical organization. Over the past two years the ambulance fleet has been updated. For the first time off-road vehicles on KamAZ chassis have been implemented into healthcare service in several areas.

Another relevant direction is the development and introduction of high technologies. In 2013 505 thousand patients received high-tech medical care (HTMC), and in 2016 this number exceeded 1 million patients. During the first 9 months of 2017 HTMC was provided to 790 thousand patients. The number of cardiac interventions including minimally invasive ones and of joint endoprosthesis replacement increased by 3 and 2.5 times, respectively. The number of hospitals providing HTMC has increased by 3.7 times, and nowadays there is no need to go to Moscow or St. Petersburg to receive complex treatment.

Prevalence of cardiovascular risk factors in Europe: data for Russia

Cardiovascular diseases (CVD) retain the leading positions in disability and mortality among the working-age population. The European Heart Agency experts annually publish the Atlas of the European Society of Cardiology (ESC) on CVD statistics in 56 member countries [3]. In 2017 the main aim of this document was to compare indicators between high-income and middle-income countries in populations in the age range of 20–79 years. The data from WHO, the World Bank and the Health Assessment Institute were taken as the source for CVD risk factors, prevalence, and mortality.

High-income countries include Western Europe and Scandinavia, the group of middle-income countries consists of Russia, Turkey, Kazakhstan, Azerbaijan, Belarus, and the Balkans, whereas low-income countries include Georgia, Armenia, Kyrgyzstan, and Ukraine. Performed statistical analysis is gender-sensitive.

Russia takes the 7th position in terms of the prevalence of arterial hypertension (AH) (24 % among women and 34 % among men, respectively), following the former CIS countries (Estonia, Lithuania, Moldova, Belarus). The lowest frequency of AH was detected in England, Italy, Israel, and Greece.

The countries of Northern Europe are the leaders in the prevalence of hypercholesterolemia. Russia takes an average place among the analysed countries. Hypercholesterolemia is detected in 12% of female cases and in 18% of male ones. According to the results of Russian epidemiological studies the average prevalence of hypercholesterolemia in adults is about 50% (total cholesterol level>5 mmol/L).

In 2017 the highest prevalence of diabetes mellitus type 2 (DM type 2) was registered in the countries of the Middle East and Turkey. In Russia its prevalence is around 5%. These data differ from official national statistics in the direction of decrease.

Russia is among the top five countries-members of the ESC in terms of the prevalence of obesity [3]. Turkey takes the first position, and it is followed by England and Lithuania. The frequency of obesity among women is higher than among men. Among men, one in five is obese, whereas the incidence of obesity in females is 27%. In general, the high incidence of obesity prevails in the CIS countries and Eastern Europe.

Even though in recent years active work to combat tobacco consumption has been conducted in our country, Russia remains the leader in the frequency of smoking: its incidence in men reaches 55%, and in women its frequency is around 16%.

Despite the existing stereotypes, Russia does not stay among the first top ten European countries in terms of alcohol consumption. Lithuania takes the leading position (15 litres per year per person), whereas the average volume of alcohol consumption in France, Germany, and England is around 11 litres, and in Russia this value is around 10 litres. The frequency of alcohol abuse in men and women is 32% and 12%, respectively.

In terms of the frequency of insufficient physical activity Russia ranks last, being the best indicator comparing with other European countries. The lowest physical activity was registered in Malta, Serbia,

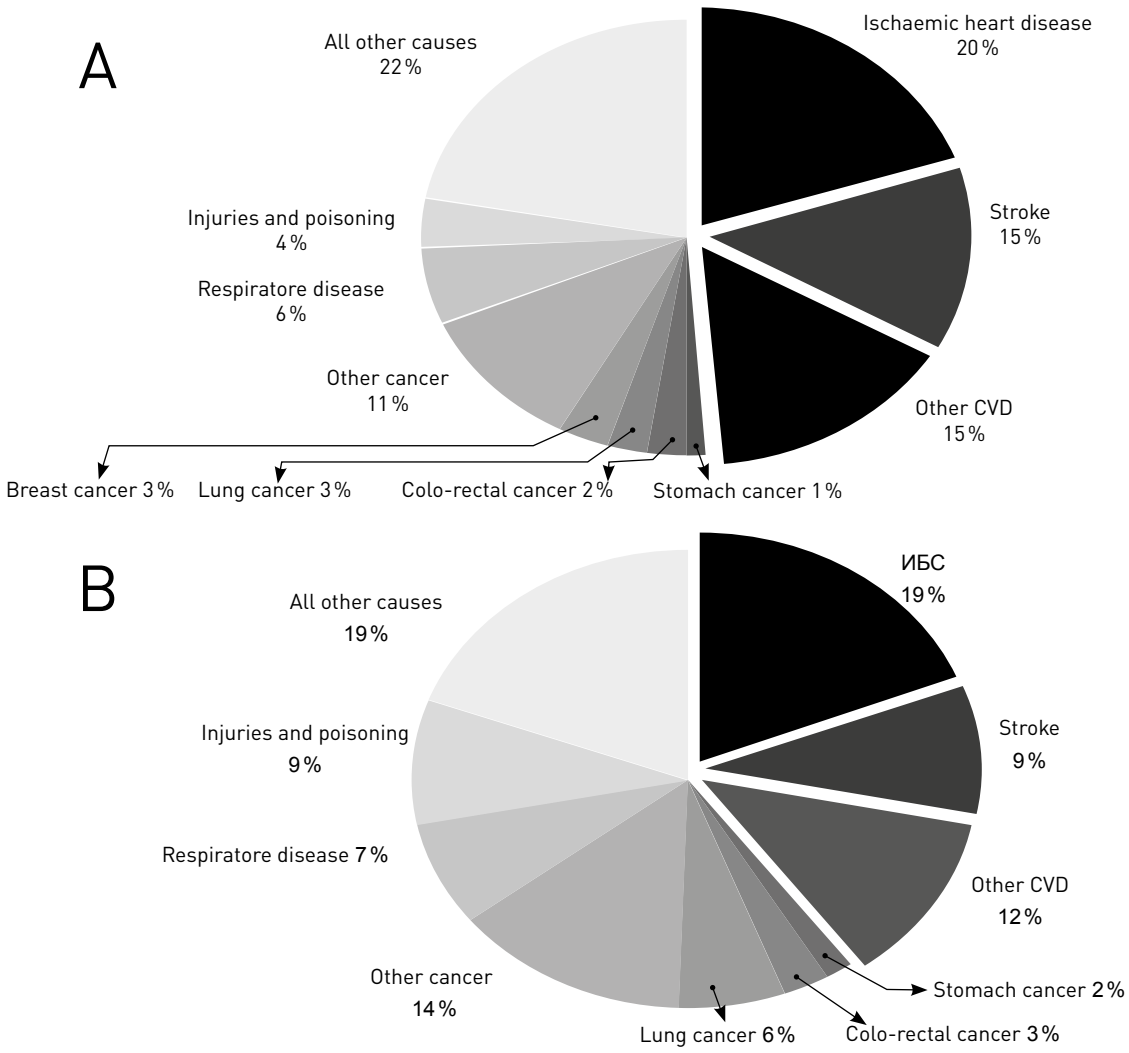

Figure 1. Causes of mortality in women (A) and men (B) in ESC member countries. Data for 2017

England and other western countries (45–50 % among men and 35 % among women). In Russia insufficient physical activity was detected in 13 % of males and 10 % of females.

In general, middle-income countries are characterized with stable indicators of CVD or their slight increase over the past 10 years, and similar situation is observed in high-income countries.

CVD and their complications remain the main causes of mortality both in men and women [3]. For example, coronary heart disease (CHD) is the cause of death in 20 % of female cases and 19 % of male cases, whereas stroke is the death cause in 13 % of women and 9 % of men. In general, the total percentage of CVD-related death causes in women and men was 48 % and 40 %, respectively.

According to the national statistical organizations, age-standardized mortality from CHD is still high in the CIS countries (Belarus, Kyrgyzstan, Moldova, Russia, and Ukraine) representing > 500 cases per 100.000 people among women and > 800 cases per 100.000 people among men, whereas in Western Europe these values are <60 (per 100.000 people) among women and <120 (per 100.000 people) among men. The same trend is observed in mortality due to cerebral stroke (>300 cases per 100.000 people in the CIS countries and <60 cases per 100.000 people in Western Europe).

Conclusion

Thus, as the result of the introduction of high technologies and realization of CNID prevention including the prophylactic medical examination program, stabilization and slight decrease of cardiovascular morbidity and mortality are noted in Russia. Together with it, there is a lot of work to be done on primary and secondary prevention of CVD including the correction of risk factors and availability of medical care.

Conflict of interests: None declared.

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Arterial stiffness in routine clinical practice: what is important to know for a clinical practitioner

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Change of elastic properties of arterial wall has an important meaning for pathogenesis of lesions of all organs in arterial hypertension (AH). This article reviews all parameters characterizing vascular elasticity, approaches to their measurement and prognostic value. These parameters include ankle-brachial index, pulse pressure, augmentation index, pulse wave velocity in aorta, and cardio-ankle vascular index. Moreover, this article considers information about the use of mentioned parameters for evaluation of cardiovascular risk and control of therapy in different categories of patients.

Keywords: *Arterial stiffness, ankle-brachial index, pulse pressure, augmentation index, pulse wave velocity in aorta, cardio-ankle vascular index*

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Relevance

A wide range of measures aimed at combating cardiovascular mortality has brought to its gradual decrease in recent years [1]. However, cardiovascular disease (CVD) continues to be the leading cause of death in the Russian Federation. Thus, according to the Federal State Statistics Service 940.5 thousand people died from CVD in 2015, representing more than half from total number of deaths [2].

Nowadays the fight against CVD is based on the "risk factor concept", which aims to identify people with high

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probability of developing cardiovascular system disease and to subsequently perform preventive measures [3]. With a certain degree of conditionality, all preventive measures can be divided into two groups: primary preventive measures and secondary preventive measures. To a large extent the latter ones represent the direct subject of activity of a practicing physician. One of the factors influencing secondary prevention efficiency is the timing of its starting. Accordingly, the early identification of subclinical lesions of target organs becomes crucially important meaning detection of such health condition of an individual when the risk factors have already influenced it in negative and often irreversible way. Subclinical markers of CVD include left ventricular myocardial hypertrophy (LVH), chronic cerebrovascular disease, chronic kidney disease stage 3, albuminuria, and retinopathy. The lesions of vascular wall being a target organ by itself have an important meaning in pathogenesis of various organ lesions. Subclinical markers of vascular wall lesions include the calcification of coronary arteries, the presence of atherosclerotic plaques in coronary arteries, increased arterial stiffness, augmentation of central blood pressure (BP), decreased ankle-brachial index, etc. Recently, most attention has been given to the evaluation of arterial stiffness due to its role in CVD development.

The damaging effects of high vascular stiffness on organs are closely associated with impaired damping function of the arterial system, which smooths out pressure fluctuations caused by cyclical ejection of blood from the left ventricle and transforms pulsating arterial blood flow into continuous blood flow required for peripheral tissues. Impaired damping function of the arterial system leads to several pathophysiological events increasing CVD risk. These events include elevated systolic blood pressure (SBP) that occurs due to lack of transformation of the kinetic energy of left ventricular blood flow into the potential energy of stretching aortic wall. It increases left ventricular afterload that leads to LVH, elevates oxygen consumption, impairs diastolic function, decreases cardiac output and in the end results in development of chronic heart failure. More than that, increased velocity of shock and reflected waves propagation through rigid vessels shifts the time of reflected wave return from diastole to late systole being the cause of decreased diastolic BP (DBP) and resulting in decreased coronary perfusion. Lowered DBP and elevated SBP together lead to the increase of pulse pressure (PP) which accelerates arterial lesions and is associated with target organ lesions [4].

Methods of vascular stiffness evaluation

In clinical practice arterial stiffness can be evaluated using various techniques. Nowadays the most studied ones include PP, ankle-brachial index (ABI), augmentation index (AI), aortic pulse wave velocity (APWV), cardio-ankle vascular index (CAVI).

PP is one of the first parameters that estimates arterial stiffness. The mechanism of PP elevation as the consequence of increased arterial stiffness is described above. In 1994 S. Madhaven demonstrated for the first time that PP>63 mm Hg has negative influence on the coronary heart disease (CHD)-related mortality of patients with arterial hypertension (AH) [5]. The Framingham heart study provided convincing evidences of the negative influence of high PP on prognosis of patients with cardiovascular pathology [6]. It was demonstrated that the coronary risk was significantly elevated and correlated with target organ lesions in case of SBP levels between 130- and 170-mm Hg and increased PP. The PIUMA study [7] demonstrated a high prognostic value of the average PP, in particular, its increase above 53 mm Hg led to five-fold elevation of the risk of all cardiovascular complications. Another study showed a stronger correlation between left ventricular myocardium mass index with PP rather than peripheral BP [8]. Low cost and high availability of the use of PP for arterial stiffness evaluation is another advantage of this technique. At the same time, PP levels depend on stroke volume, heart rate and initial BP levels that restricts the applicability of this parameter especially in young patients with hyperkinetic circulation type.

Estimation of ABI is another simple and available method of vascular stiffness evaluation. ABI reflects the ratio of SBP measured at the ankle to SBP measured in the upper arm. ABI decrease below 0,9 is a predictor of CHD, stroke, transitory ischemic attacks, renal failure, and total mortality [3]. It is necessary to highlight that neither ABI nor PP may be considered highly specific markers of arterial rigidity since they are influenced by atherosclerotic lesions of the lower limbs [9].

AI is a less studied criterion of arterial rigidity comparing with ABI and PP. Nevertheless, the existing data demonstrate that it may be used as an independent predictor of coronary events and significantly correlates with the degree of LVH [10]. However, AI has an independent predictive value for prognosing the risk of total mortality in patients with established CHD diagnosis [11].

According to some data [12], AI elevation may be diagnosed even before the identification of such indi-

cators as increased thickness of the carotid intima-media complex and decreased endothelium-dependent vasodilation. AI can be determined by recording and subsequent automatic analysis of the sphygmogram. This feature is realized in such devices as the VaSera VS-1500N volumetric sphygmograph and the BpLab 24h-blood pressure monitoring system with Vasotens extension.

The positive aspects of AI, as a method for assessing vascular stiffness, should include high sensitivity as well as variability in response to therapy. The results of our own observations confirm the high value of the method for the assessment of antihypertensive therapy effectiveness [13]. The negative side of the method is its dependence on heart rate and baseline BP. Another important disadvantage is the lack of reference values. It is only known that the AI measured on the brachial artery should be in the range of negative values.

APWV evaluation is rightly considered to be the "golden standard" for assessing vascular stiffness. Measuring the characteristics of wave propagation along the aortic pathway is the most appropriate from clinical point of view, since the aorta and its main branches are responsible for most of the pathophysiological effects of arterial stiffness. According to the guidelines of the American Heart Association, arterial stiffness should be measured noninvasively via carotid-femoral pulse wave velocity (PWV) evaluation [14, 15]. APWV in other segments like ankle-brachial one may be useful, but currently no long-term study of this method is available in the USA or in Europe. The determination of PWV in other arterial segments like carotid-radial one is not recommended since it has no prognostic value.

The prognostic value of APWV evaluation in terms of cardiovascular risk has a wide evidence base. 5-year observation on patients with AH demonstrated the increase of the risk of cardiovascular complications and death by 1,4 times for each increase of APWV by 3,5 m/s independently from any other known risk factor [16]. Some authors consider that APWV correlates with the risk of acute myocardial infarction, acute cerebrovascular accident, cardiovascular and total mortality more tightly than age, BP levels, smoking, LVH, and CHD [17].

Different approaches for wave registration can be used for APWV measurement. The corresponding sensors can reflect the pressure, the dilation of the arterial wall, and the blood flow velocity measured by the Doppler method. The path travelled by the wave is usually equated to the surface distance between the two registration areas.

A piezoelectric tonometer is used in the methods based on applanation tonometry (for example, the "traditional" SphygmoCor device). The SphygmoCor device has been used in studies of arterial wall stiffness in chronic kidney disease, as well as in some other studies. Since January 2016 the SphygmoCor technology has been approved for measuring CBP, AI, APWV in routine clinical practice in the USA, and the costs are reimbursed by insurance companies.

The Complior system is an example of devices using mechanical sensors for registering pulse waves. This technique has been used in most epidemiological studies that have demonstrated the prognostic value of APWV for cardiovascular events.

One type of the devices registering arterial wall oscillations is volumetric sphygmometers equipped with 4 oscillometric cuffs located on both hands and ankles (Omron VP1000, VaSera VS-1500N, ABI-system 100). In addition, the system for 24h BP monitoring BpLab with Vasotens extension is also able to calculate APWV by registering a sphygmogram at one point using a specific mathematical algorithm.

Despite the large evidence base, it is necessary to emphasize some limitations of the use of APWV for evaluation of arterial rigidity. In particular, some difficulties preventing high-quality registration of pressure pulse waves with mechanical sensors and applanation tonometry on femoral artery may occur in patients with metabolic syndrome, obesity, diabetes mellitus and peripheral artery disease [18]. The presence of aortic, ileal or proximal femoral stenosis can distort the results of any measurement method. Abdominal obesity especially in men and large breast in women lead to errors in measuring the distance between two registration points [19]. It requires precise measurement of the distance because even small errors may influence the absolute values of APWV [20]. Different researchers recommend either using the total distance between registration points on the carotid and femoral arteries or subtracting the distance from the carotid artery to the jugular notch from the total distance or subtracting the distance from the carotid artery to the jugular notch from the distance between the jugular notch and the measurement site on the femoral artery [19]. All three options allow only approximate estimation of the distance which is irrelevant for the studies aiming at identifying difference between the original and repeated measurements. However, the differences in distance measurement

methods become critically significant in comparison of the results of different studies, and it imposes certain restrictions on the use of this method. In addition, APVW values depend on initial BP levels.

In recent years, CAVI, a new marker of high vascular stiffness, which does not depend on the initial BP levels, has attracted increasing attention. It is proved that the level of CAVI reflects the severity of coronary atherosclerosis in patients with established CHD [21]. Angiographic studies demonstrated that CAVI increases proportionally with the number of coronary arteries affected with atherosclerotic lesions [22], as well as the extent and the degree of stenosis [21]. More than that, CAVI is an independent parameter positively associated with the coronary calcium score and the degree of coronary stenosis [23]. There is a significant correlation between CAVI and severity of atherosclerosis in the carotid arteries in patients with cerebrovascular disease [24].

CAVI measurement is performed using a VaSera VS-1500N volumetric sphygmograph. Apart from CAVI, this device can measure ABI, AI, and APWV. Simultaneous analysis of the main markers of high vascular stiffness allows using this device for screening of subclinical vascular lesions. It should also be noted that according to the order of the Ministry of Health of the Russian Federation dated December 26, 2016. No. 997n "On Approval of the Rules for Functional Diagnostics", volumetric sphygmometers are included in the equipment standard of the functional diagnostics department.

Concluding the discussion of the methods of vascular stiffness evaluation, we would like to emphasize that the above-mentioned markers of arterial rigidity do not substitute each other and have independent prognostic significance, and, consequently, their complex evaluation is necessary for more accurate evaluation of cardiovascular risk in concrete patient.

Clinical significance of evaluation of vascular stiffness

In general, evaluation of arterial stiffness may be used ad a screening approach for subclinical atherosclerosis detection and determination of the groups of high cardiovascular risk. Detection of subclinical lesions of vascular wall in patients without CVD aiming to modify lifestyle and to prevent further structural and functional lesions of target organs has a high value.

Arterial stiffness has an independent prognostic value in relation to fatal and non-fatal cardiovascular events in patients with AH [3, 25]. The results of arterial stiffness measurement demonstrated that a significant part of AH patients with moderate cardiovascular risk could be reclassified as high cardiovascular risk patients.

It has been established that decreased vascular elasticity indicates atherosclerosis progression and is associated with global severity of atherosclerotic process in patients with CHD and peripheral artery disease [26].

The brain is particularly sensitive to the decrease of vascular elasticity and, as a consequence, to a more pulsating blood flow [4]. Local circulation is connected with low resistance of microvessels which facilitates the transmission of excessive energy of the pulsating flow to the microvascular bed [27]. This may contribute to recurrent episodes of microvascular ischemia, tissue damage and is manifested as white matter tension, clinically unconfirmed focal brain infarction and tissue atrophy that contributes to the development of cognitive impairment and dementia. Aortic stiffness is also associated with increased risk of ischemic or haemorrhagic stroke [28].

Arterial stiffness is tightly related to decreased glomerular filtration rate and is a predictor of progressing kidney lesions up to terminal kidney insufficiency requiring dialysis [29]. Increased vascular stiffness is associated with higher risk of albuminuria and its progression [30]. High arterial rigidity is a potent independent predictor of total and cardiovascular mortality in the population of patients with chronic kidney disease [31].

The above-mentioned data suggest the high prognostic value of arterial stiffness markers for determination of total cardiovascular risk in different categories of patients. However, apart from solving the problems related to cardiovascular risk estimation, arterial rigidity markers can be used for therapy control. Even though nowadays there is no convincing evidence of improved prognosis associated with decreased arterial stiffness, it can be assumed by analogy with LVH, and these data will be available soon. In this regard, reduction of vascular stiffness should become a separate goal (intermediate endpoint) of therapy of patients with CVD together with reaching target levels of BP, cholesterol, cardio- and nephroprotection, etc.

Among the non-pharmacological approaches influencing vascular wall in a positive way, moderate physical activity, weight loss, low-salt diet, moderate

alcohol consumption, intake of garlic, fish oil, and α-lynoleic acid should be mentioned [32].

Pharmacological agents with a proved effect of decreased vascular remodelling include angiotensin-converting enzyme inhibitors, angiotensin receptor type II blockers, calcium channel blockers, several beta-blockers with vasodilating effects, indapamide, nitrates, and statins [33, 34, 35]. The results of our study [13] demonstrate a higher efficiency of a fixed combination of amlodipine and lisinopril comparing with metoprolol monotherapy.

Conclusion

Thus, nowadays practicing doctors have a sufficient number of methods evaluating arterial stiffness. These methods include some available markers (PP and ABI) and more sensitive and specific ones (AI, APWV, CAVI) requiring, however, additional equipment. The use of the above-mentioned vascular stiffness indicators in routine clinical practice for estimation of cardiovascular risk and therapy efficiency, undoubtfully, should contribute to increased quality of medical care for CVD patients.

Conflict of interest: None declared

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EXPERT OPINION

New EHRA guidelines on anticoagulant therapy in patients with atrial fibrillation: comments of Russian experts

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The experts of the European Heart Rhythm Association prepared new guidelines on oral anticoagulant therapy in patients with atrial fibrillation. These guidelines included a wide spectrum of practical aspects of the use of anticoagulant therapy. This document provides comments of the leading Russian experts on four main directions: general aspects of the use of new oral anticoagulants (NOA), control of NOA efficiency, NOA adverse effects and management of complications of NOA therapy, and practical aspects of NOA therapy in several groups of patients.

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The Congress of the European Heart Rate Association (EHRA) was held in Barcelona (Spain) on March 18–20, 2018, within the framework of which new guidelines on oral anticoagulant therapy in patients with atrial fibrillation were presented [1]. The document consists of 20 chapters that can be combined into 4 main areas: general aspects of the use of new oral anticoagulants (NOAC), monitoring of NOAC effectiveness, NOAC side effects, the elimination of complications, and practical aspects of the use of NOAC in certain groups of patients.

The leading Russian experts gave their comments on topical issues of NOAC use in patients with atrial fibrillation (AF) that are listed here below.

General aspects of NOAC use in patients with atrial fibrilation

Sergei G. Kanorskii (Krasnodar)

The process of NOAC expansion in the field of thromboembolism prevention, in particular, in AF patients is unfolding before our eyes. It can be expected that in the near future, the use of NOAC will be impossible only in patients with AF and mechanical valve prostheses, moderate/severe rheumatic mitral stenosis [2]. In the new edition of the EHRA guidelines, it is allowed to use NOAC in patients with AF and bioprosthetic heart valves, after surgical correction of mitral defect, and transcatheter implantation of the aortic valve.

The indication on the necessity of regular (at least once per year) monitoring of patients taking NOAC (assessment of haemoglobin levels, liver and kidney function) should attract physicians' attention. Laboratory blood tests should be carried out even more frequently in patients with reduced kidney function, in elderly and old people. At the same time, in daily work, clinical practitioners evaluate patients' kidney function by calculating glomerular filtration rate, whereas during large randomized NOAC-dedicated studies, renal function was determined by the creatinine clearance (using the Cockroft-Gault formula). Neither NOAC can be prescribed in case of creatinine clearance < 15 mL/min due to its accumulation in the body and consequently high risk of the haemorrhage. Reduced doses of rivaroxaban (15 mg once per day) or apixaban (2.5 mg twice per day) can be used in case of creatinine clearance of 15-30 mL/ min. Dabigatran cannot be used with creatinine clearance <30 mL/min, but within the values of 30-50 mL/min, its prescription in doses of 110 or even 150 mg is acceptable (depending on the risk of bleeding) 2 times per day (Figure 1).

It is necessary to withdraw NOAC 24-48h before any surgical intervention depending on bleeding risk.

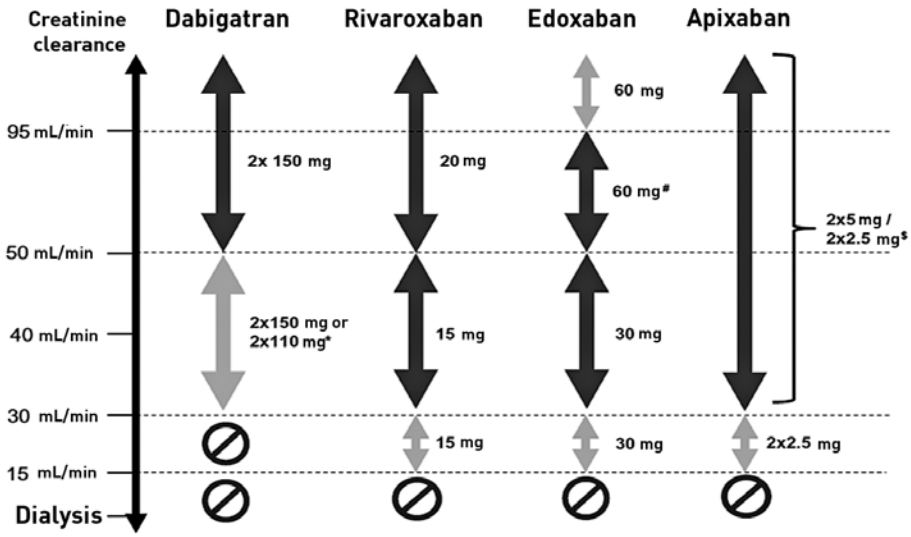


Figure 1. NOAC use depending on creatinine clearance

Meanwhile, in patients with chronic kidney disease (CKD) receiving dabigatran, the period between its cancellation and the surgical procedure should be, 48-96h, depending on the creatinine clearance.

In case of acute coronary syndrome (ACS) in a patient taking NOAC, percutaneous coronary intervention can be performed immediately, preferably using radial access. The duration of dual antiplatelet therapy after percutaneous coronary intervention in patients receiving NOAC should be reduced (no more than 3 months). After a period of dual therapy (NOAC + clopidogrel up to 12 months after percutaneous coronary intervention), which can also start directly after percutaneous coronary intervention, patients should be transferred to NOAC monotherapy.

NOAC therapy should be considered for resumption 3-14 days after ischemic stroke, depending on the degree of neurological deficiency and after exclusion of haemorrhagic transformation according to the results of computed tomography scan of the brain.

By now NOAC use in several clinical situations has not been well studied in major randomized clinical studies. Therefore, the updated European Heart Rhythm Association practical guidelines for the use of NOAC in patients with AF allow practitioners to make decisions in accordance with the consistent opinion of leading experts.

Control of NOAC efficiency

Sergei R. Gilyarevskii (Moscow)

Transfer of patients to another regimen of anticoagulant administration

When transferring patients from the use of one anticoagulant to the use of another one, one should be convinced of the continuity of anticoagulant therapy minimizing the risk of bleeding at the same time. Pharmacokinetic and pharmacodynamic features of various anticoagulants therapy regimens should be interpreted considering individual patient's characteristics [1].

Transfer from vitamin K antagonist (VKA) to a new oral anticoagulant (NOAC)

NOAC can be prescribed immediately if international normalized ratio (INR) is less than 2.0. If the INR corresponds to a range of 2.0-2.5, NOAC therapy can be started immediately or (preferably) the next day. If the INR is above 2,5 it is necessary to take into account both the INR values and the half-life of VKA in order to calculate the period during which the INR drops below the threshold level (the half-life of acenocoumarol, warfarin, phenprocoumon is 8-24, 36-48 and 120-200h, respectively).

The suggested scheme of transfer based on data from the patient information leaflets for these drugs is present on Figure 2. Briefly, NOAC administration may be started with the INR of 3.0 or less for rivaroxaban, 2.5 or less for edoxaban, and 2.0 or less for apixaban and dabigatran.

Transfer from NOAC to VKA

Given the slow onset of VKA action, it may take 5–10 days to reach the therapeutic range of INR; and this period can have significant individual variability. Therefore, NOAC and VKA should be administered contemporaneously until the INR reaches adequate therapeutic range. This approach is similar with the one used for administration of low molecular weight heparin (LMWH) together with the start of VKA treatment. Administration of the saturating dose of acenocoumarol and warfarin is not recommended, but such a method is acceptable when using fenprocoumone.

It should be remembered that NOAC administration may affect the results of INR measurement, therefore, it is important to follow these conditions: 1) The INR should be measured immediately before taking the next dose of NOAC during the combined therapy with VKA and NOAC; 2) The INR should be remeasured at early period after the cessation of NOAC therapy (in order to evaluate exclusively the effects of VKA administration) to prove the efficiency of anticoagulant treatment. Additionally, it is recommended to carefully monitor the INR levels during the first month until stable results are obtained (for example, INR in the range between 2,0 and 3,0 according to 3 consecutive analyses).

If combined use of NOAC during the start of VKA therapy is supposed to be inappropriate, during the initial period of VKA administration it is possible to temporally transfer the patients from NOAC to LMWH, that can be considered in several occasions, particularly in patients with high risk of developing thromboembolic complications.

Transfer from NOAC parenteral administration of anticoagulants

Parenteral administration of anticoagulants (unfractionated heparin – UFH) and LMWH can be started at the moment of suggested administration of another NOAC dose.

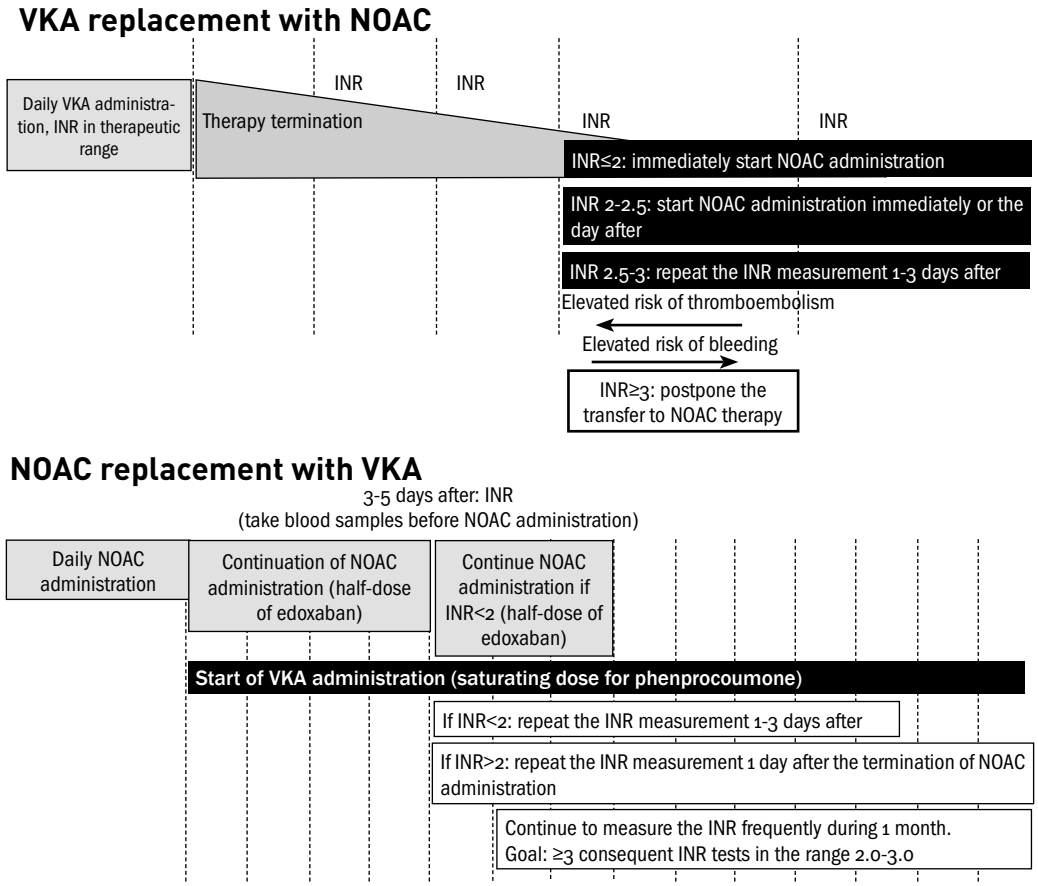


Figure 2. The scheme of NOAC replacement with VKA and vice versa.

Transfer from parenteral administration of anticoagulants to NOAC

Intravenous administration of UFH: NOAC administration normally may be initiated 2h (up to 4h after) after termination of UFH intravenous administration (half-life period of 2h).

LMWH: NOAC therapy may be started at the time of suggested administration of the next dose of LMWH. This requires particular caution in patients with impaired kidney function, since the time of LMWH elimination in these patients may be extended.

NOAC use in patients with CKD

Cinical decision on the tactics of treating a patient with AF in the presence of CKD, who needs to receive anticoagulants, should be based on the results of renal function assessment [3]. Several formulas are used for evaluation of kidney function, and each of them has distinct advantages and disadvantages. The CKD-EPI formula is recommended for calculating glomerular filtration rate (GFR) by the experts of the National Kidney Foundation, since its use provided reliable results for different stages of CKD. In case of NOAC administration it is more preferable to evaluate kidney function through creatinine clearance calculated with the Cockroft-Gault formula that has been used in numerous clinical studies. It is worth to highlight that it is possible to establish CKD diagnosis and to define its severity only in case of stable renal function but not in case of acute renal failure. In the latter case, creatinine level in the blood and calculated creatinine clearance may indicate only moderately reduced (or even normal) kidney function not reflecting the real severity of existing abnormalities. In case of acute renal failure NOAC therapy should be discontinued, and parenteral anticoagulant therapy should be prescribed (after careful comparison of risk and benefits).

Patients taking NOAC should be carefully monitored for renal function that should be evaluated not less frequently than once per year to detect changes in kidney function and perform adequate dose correction. If kidney function is impaired (if creatinine clearance is 60 mL/min and less) it is recommended to estimate renal function more often (the minimal frequency of these tests can be calculated using the following formula: creatinine clearance/10). Renal function should be assessed more frequently if additional risk factors (elderly age, weakness, several concomitant diseases, etc) are present, particularly

in case of treatment with dabigatran. Development of concomitant diseases (infections, acute heart failure, etc) may temporarily influence the kidney function, and it should be evaluated in such cases. Patient should know about the necessity of medical consultations in these situations.

It is worth to mention possible decrease of edoxaban (60 mg once per day) efficiency comparing with warfarin in patients with creatinine clearance ≥ 95 mL/min. Moreover, the results of secondary data analysis in patients included in studies dedicated to rivaroxaban and apixaban showed a similar pattern.

NOAC use in patients with mild or moderate CKD (creatinine clearance 30 mL/min or more)

According to the analysis of the main clinical trials of NOAC, the use of all 4 NOAC in patients with mild or moderate CKD is associated with stable efficiency and safety comparing with warfarin, similar with the treatment in the absence of CKD.

Moreover, the results of the ARISTOTLE study suggest a lower risk of bleeding when using apixaban compared with warfarin in these patients; and such benefits of apixaban became significantly more evident in case of lower creatinine clearance while maintaining benefits in reducing the risk of stroke [4]. On the contrary, the advantages of using 110 mg dabigatran compared with warfarin disappeared in patients with creatinine clearance less than 50 mL min while maintaining a similar risk of developing stroke compared with warfarin.

Using an appropriate dose of NOAC is particularly important for CKD patients. Despite the fact that rivaroxaban, apixaban and edoxaban doses were reduced according to kidney function in major randomized clinical trials (RCT), the RE-LY study randomized patients into the groups receiving dabigatran in dose of 150 mg twice per day or 110 mg twice per day without dose reduction in case of absence of renal failure [4]. It is recommended to use dabigatran in the dose of 110 mg twice per day in patients with creatinine clearance below 50 mL/min and high bleeding risk. Given the availability of 3 inhibitors of Xa factor, which are less excreted by the kidneys, the use of these drugs is preferable in patients with impaired renal function. NOAC use in doses not corresponding to indications correlates with worse prognosis. In particular, apixaban use in patients with normal renal function or its mild impairment was associated with decreased efficiency (increased frequency of stroke) and lack of information about higher safety in group of patients with AF, that are supported by some clinical evidences.

Use of anticoagulants in patients with creatinine clearance 15-29 mL/min

There are no RCT data on the effectiveness of NOAC for the prevention of stroke in patients with AF and severe CKD or in patients who use kidney replacement therapy, since the main NOAC-dedicated RCT did not include patients with creatinine clearance less than 30 mL/ min (except for a small number of patients with creatinine clearance 25-30 mL/min, who used apixaban). However, it be noted that warfarin has never been prospectively studied in RCTs, in which such patients would be included.

Rivaroxaban, apixaban, and edoxaban (but not dabigatran) are approved for using for treatment of patients with severe CKD (stage 4 with creatinine clearance 15-29 mL/min) in Europe, considering appropriate dose reduction.

NOAC use in patients with creatinine clearance less than 15 mL/min and in hemodialysis patients

Safety and efficacy of NOAC use in patients with terminal CKD and in hemodialysis patients remains unclear and is actively investigated in ongoing studies. The results of the analysis of these registers showed a higher incidence of admission to hospital or death from bleeding in patients receiving hemodialysis, that began taking dabigatran or rivaroxaban in absence of registered indications, compared with VKA.

In the USA, but not in Europe and not in Russia, apixaban (5mg, twice per day) is currently approved for use in patients with chronic CKD receiving hemodialysis. It is worth to mention some recent results indicating that in this case (apixaban dose 5mg, twice per day) blood concentration of apixaban is higher than therapeutic one.

In patients with these characteristics, the concentration of NOAC in the blood corresponded to that in patients with normal renal function if they received apixaban (2.5 mg 2 times a day, in a small number of hemodialysis patients), edoxaban (15 mg once a day, severe renal failure, Japanese study), and rivaroxaban (10 mg once a day, in patients with terminal CKD). Notably, blood concentration of a drug can be considered just an indirect indicator of its efficiency of safety. In the absence of specific RCT data assessing clinical outcomes, NOAC use should be avoided as a

standard tactic in patients with severe renal dysfunction (creatinine clearance less than 15 mL/min) and in patients receiving hemodialysis. However, given the lack of convincing data on the efficacy and safety of VKA use in this situation, the decision on the choice of anticoagulant can be individual and should be made after discussion with colleagues and considering patient's preferences.

There are no data on the use of NOAC in patients who underwent kidney transplantation. If NOAC are used in such patients, the dose should be selected in accordance with the calculated indicators of renal function; moreover, caution should be exercised due to the possibility of drug interactions between NOAC and concomitant immunosuppressive therapy.

NOAC use in patients with severe liver diseases

The use of all 4 NOAC is contraindicated in patients with liver diseases, associated with coagulopathy and clinically significant bleeding, including patients with cirrhosis, the severity of which corresponds to class C of the Child-Turcotte-Pugh classification. Rivaroxaban should also not be used in patients with AF and Child-Pugh class B cirrhosis, due to more than a double increase of blood drug concentration in such cases. Dabigatran, apixaban, and edoxaban can be used with caution in patients with class B cirrhosis. Both hepatologist and haematologist should prescribe therapy and control its effects in the conditions of specialized medical centres. None of the NOAC studies showed an increase in the risk of liver damage. According to experts, this risk may be even less than in case of VKA use.

Algorithm of NOAC dose choice considering drug interactions

A possible algorithm of the choice of NOAC dose considering drug interactions presented on Figure 3.

How to measure the anticoagulant effect of NOAC?

Aleksei V. Tarasov (Moscow)

In routine clinical practice, NOAC do not require monitoring coagulation: neither dose nor treatment intervals should not be corrected in response to the change of coagulation parameters for the registered indications. However, laboratory tests evaluating drug influence on anticoagulant effect may help clinical practitioners in case of emergency or in particular clinical situations [1].

Long-term laboratory monitoring may be considered for patients with particular characteristics (severely overweight or underweight patients, high risk

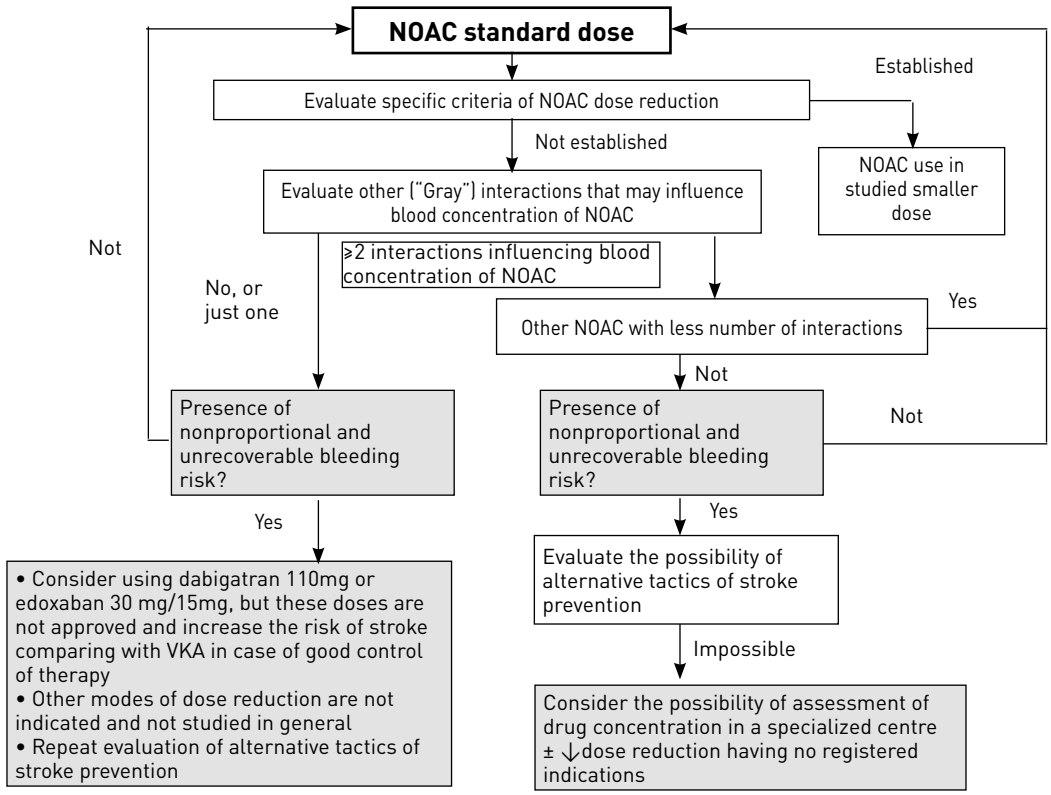


Figure 3. A possible algorithm of the choice of NOAC dose considering drug interactions

of bleeding, evaluation of compliance to treatment). Common tests of coagulation (prothrombin time (PT), activated partial thromboplastin time (APTT)) do not give a precise estimation of NOAC effects, since it can be measured just with specific anticoagulation tests developed for quantitative evaluation of NOAC in blood serum. Therefore, considering emergency situations, it is recommended to consider the opportunity of 24h-availability of these tests in all hospitals.

Chromogenic analysis of anti-Xa factor are available for measuring concentrations of inhibitors of Xa factor in blood plasm, using proved test calibrators of diluted thrombin time (dTT), and using ecarin clotting time (ECT). They demonstrate direct linear correlation with dabigatran concentration and are suitable for quantitative estimation of dabigatran concentration.

The review of expected values of maximal and minimal NOAC concentrations is presented in Table 1. It is important to know the time of NOAC administration in relation to blood sampling time for correct interpretation of the analysis of coagulation. Maximal effect of NOAC on clotting test occurs when its concentration in plasm is maximal, and it corresponds to the time interval of 1-3h after administration of each of these drugs (Figure 3).

Measurement in emergency situations

In emergency situations, such as bleeding, urgent invasive interventions or acute stroke, available routine blood clotting tests can quickly inform the doctor about the anticoagulant effect at a given point in time; specific analyses can provide an accurate assessment of drug plasma levels. Coagulation tests can also detect associated bleeding disorders, and, in exceptional cases of a planned operation with a high risk of bleeding, they can help to determine the timing of the intervention.

Dabigatran

APTT can provide qualitative estimation of dabigatran anticoagulant activity. The correlation between dabigatran and APTT is curvilinear during the day. Clinically significant plasma levels of dabigatran have a small influence on PT and INR that makes them inappropriate for evaluation of dabigatran anticoagulative activity. Thrombin time (TT) is very sensitive to the presence of dabigatran, and normal TT values exclude the presence of very small doses of this drug. dTT and ECT tests allow measuring dabigatran levels in a clinically significant range.

Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

Factor Xa inhibitors influence PT and APTT differently. But APTT cannot be used for any significant evaluation of Xa factor inhibition due to its restricted duration, high variability of analysis and paradoxal response to low concentrations. Even if factor Xa inhibitors demonstrate concentration-dependent increase of PT, this effect depends both on the inhibitor itself and on the analysis. More than that, PT is not specific and may be influenced by numerous factors (hepatic insufficiency, vitamin K deficiency, for example). PT cannot be used for estimation of anticoagulant effect of apixaban. PT may give some quantitative information for rivaroxaban and, to a lesser extent, for edoxaban, even if the sensitivity of different reagents is significantly different and may be insensitive to the effect of anti-Xa factor.

Adverse effects of NOAC and liquidation of complications

Vadim S. Zhuk (Saint-Petersburg)

Despite the absence of obligatory control and convenient therapeutic regimen of NOAC, it is impossible to exclude the errors of administration. The most frequent and the most "human" one is simple for-

Table 1. **NOAC plasma levels and appropriate clotting tests**

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Expected plasma levels of NOAC in patients with AF (based on the diluted thrombin time (dTT) /ecarin coagulation test (ECT) for dabigatran and anti-Xa factor (for Xa factor inhibitors)				
Expected plasma variation (peak) for standard dose (ng/mL)*	64–443	69–321	91–321	184–343
Expected plasma level variation (lowest, "at the bottom") for a standard dose (ng/mL)*	31–225	34–230	31–230	12–137
Expected effects of NOAC on routine clotting tests				
PT	↑	(↑)	↑(↑)	↑↑ (↑)
APTT	↑↑(↑)	(↑)	↑	↑
Activated clotting time	↑(↑)	↑	↑	↑
TT	↑↑↑↑	–	–	–

***** This variation in values is shown as P5/95 percentile for dabigatran, rivaroxaban, apixaban, and interquartile range for edoxoban

getfulness. Each patient should be informed how to proceed in case of a missed drug dose. The forgotten medication dose should be taken immediately if the half period before the next drug administration has not passed yet (12h or 6h is drug is taken once or twice a day, respectively). If this time has already passed, it is recommended to take the next dose and every effort should be made to prevent such a situation in future. Another possible mistake is taking a double dose. If drug is taken twice a day, it is recommended to skip the next administration, and if the medication regimen is once a day, treatment should be continued normally.

The situation related to increased concentration of drug in blood is potentially dangerous since it may lead to bleeding.

This is possible either if patient deliberately or not took more than three pills, or if he developed acute renal failure on the background of chronic administration, or if it was the result of drug interactions. In case of overdose, some coagulation tests may help. For example, normal APTT excludes high level of dabigatran, and normal PTT excludes overdose of rivaroxaban, apixaban, and edoxaban.

In general, NOAC are safe enough, however, their administration increases the absolute number of bleeding cases. The relevant sections of the guidelines are dedicated to evaluation of the risk of bleeding. If bleeding occurs, it is important to understand rapidly how much threatening it is for patient's life: if it is small and not dangerous or if it is large and life-threatening. In addition, it is necessary to obtain information about what particular drug and in which dose the patient is taking, the exact time of the last dose, renal function, and concomitant therapy. Remembering the relatively short NOAC half-life period, waiting strategy is adopted, otherwise the need to administer a specific drug inhibitor is considered.

Minor bleeding during NOAC therapy can be normally resolved by skipping one dose, at maximum. In case of recurrent bleeding, it is acceptable to reduce the dose or replace the drug with another NOAC with a different mechanism of action. However, in case of a larger but still not life-threatening bleeding some measures aiming to treat the underlying cause of bleeding, like mechanical compression, endoscopic or surgical hemostasis, etc, are required. Already at this stage, the possibility of dialysis or of administration of a specific antidote should be planned. In life-threatening situations, the use of antidotes and other specific medications can bring significant benefits and reduce potential danger. The detailed algorithm is presented at Figure 4.

NOAC therapy may be resumed in most of cases after stopping bleeding and eliminating its cause. All other bleeding cases, especially the life-threatening ones, require the re-evaluation of benefits and risks of repeated start of anticoagulant therapy. Especially

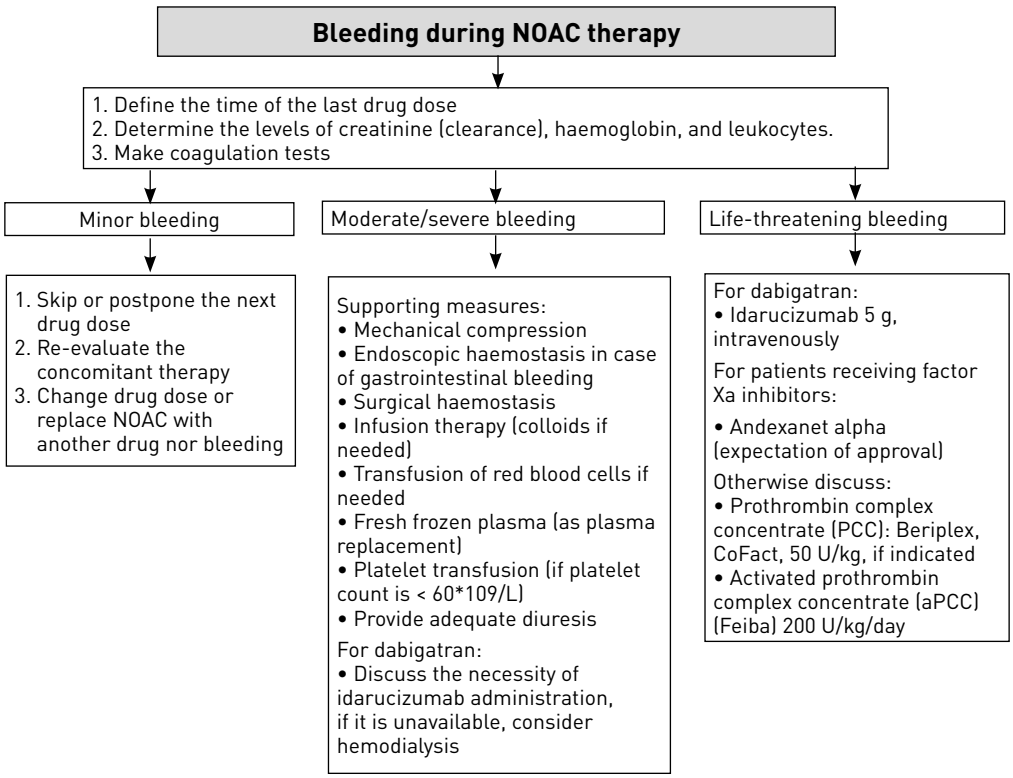


Figure 4. Algorithms of actions in case of bleeding during NOAC therapy

after severe and life-threatening bleeding, the risks of re-initiating anticoagulant therapy may outweigh the benefits. In such cases, implantation of the occluder into the left atrial appendage can be considered as a potential substitute for long-term anticoagulation.

Practical aspects of NOAC use in some groups of patients

Igor S. Yavelov (Moscow)

Percutaneous coronary interventions in patients with AFT taking NOAC

The approach to NOAC therapy of patients with stable coronary heart disease (CHD) undergoing transcutaneous coronary interventions (TCI, coronary stenting) is shown in Figure 5. It has few differences from the previous version of this guideline. The main difference is that it is recommended to check NOAC levels in blood and not routine clotting parameters when deciding on thrombolytic therapy and parenteral anticoagulant administration during thrombolysis.

Comments: ATT – antithrombotic therapy, ACT – activated clotting time, GP IIb/IIIa inhibitors – glycoprotein IIb/IIIa inhibitors; MI w– myocardial infarction; PPI – proton-pump inhibitors; LMWH – low molecular weight heparin; UFH – unfractionated heparin; DES – drug-eluting stents.

Many aspects of the use of combined antiplatelet therapy after PCI are unclear [1]. This concerns both its duration and its composition. The decision must be made individually, taking into account the characteristics of a particular patient. The algorithm proposed in this document assumes the use of triple antithrombotic therapy within 1-7 days after PCI (prior to discharge). In the future, after the implantation of modern DIS in patients with stable CHD, it is preferable to use double antithrombotic therapy (NOAC in combination with aspirin or clopidogrel) up to 1 year, then changing it for NOAC monotherapy. Such approach is acceptable for PCI in patients with ACS, but in this case also the triple antithrombotic therapy with duration of 3 months is considered (that is less than in guidelines of other expert groups recommending 6 months of triple antithrombotic therapy). The arguments favouring reduced duration of double/triple antithrombotic therapy are unavoidably high risk of bleeding and low atherothrombotic risk. The reasons for increased duration of double/triple antithrombotic therapy include implantation of first-generation drug-eluting stents, high atherothrombotic risk (stenting of the left coronary artery, proximal stenosis of the anterior interventricular branch, and proximal bifurcation, repeated MI history, history of stent thrombosis) together with the low risk of bleeding. In patients with a score on the scale CHA2DS2-VASc = 1 in men or =

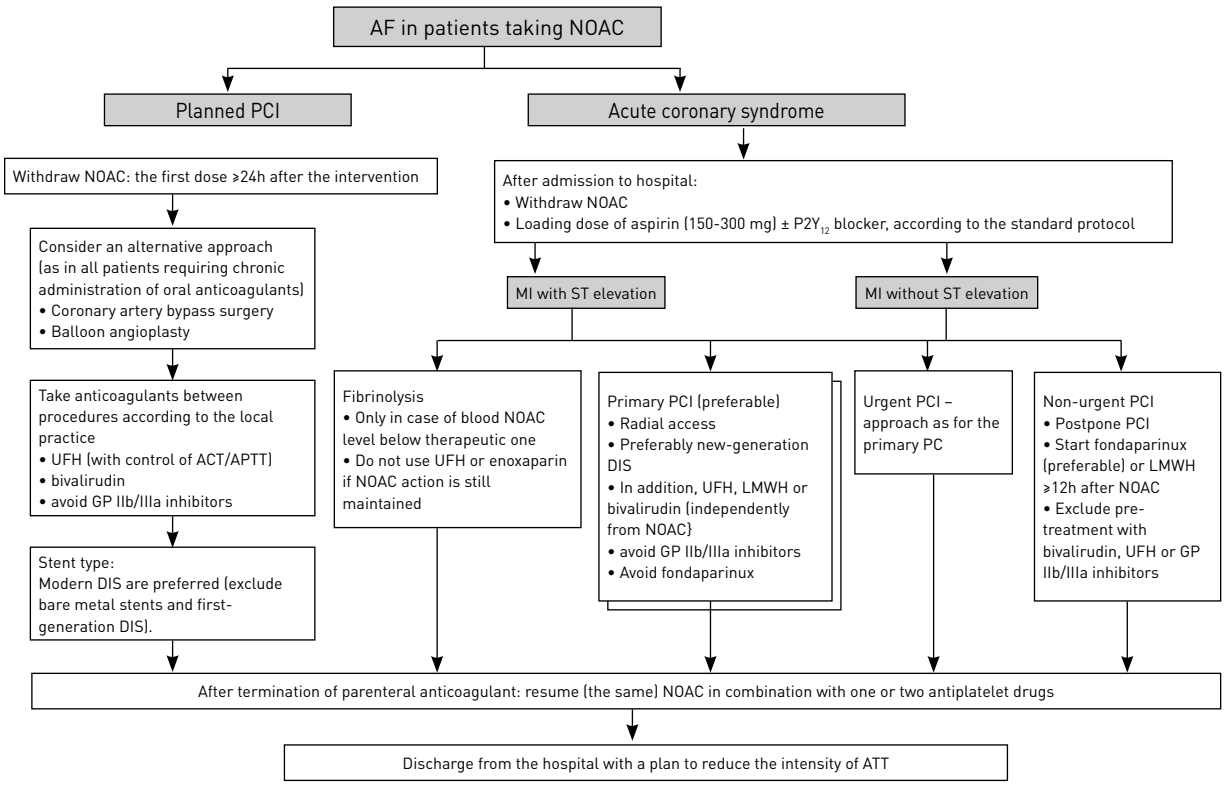


Figure 5. PCI in patients with AF taking NOAC

Table 2. **Timing of the last dose of NOAC before the start of planned invasive interventions.**

Creatinine clearance (mL/min)	dabigatran etexilate		Apixaban, rivaroxaban, edoxaban	
	In the absence of a significant risk of bleeding and / or adequate local hemostasis, a procedure is possible when minimal drug concentration in the blood is reached (in particular, 12 or 24 hours after the last dose)			
	Low bleeding risk	High bleeding risk	Low bleeding risk	High bleeding risk
≥80	≥24 h	≥48 h	≥24 h	≥48 h
50-80	≥36 h	≥72 h	≥24 h	≥48 h
30-50	≥48 h	≥96 h	≥24 h	≥48 h
15-30	Not indicated		≥36 h	≥48 h
<15	No official permission for use			
Bridge therapy using LMWH/UFH is not needed				
Resume taking full NOAC dose ≥24h after interventions with low risk of bleeding, and 48(-72h) after interventions with high risk of bleeding				
In case of planned operations patients should receive written instructions where the expected date and time of the intervention are mentioned together with the timing of the last NOAC dose (and other medications)				

2 in women, in combination with an increased risk of bleeding, it is suggested to refuse NOAC therapy limiting treatment to antiplatelet agents.

NOAC doses after PCI in patients with non-valvular AF: apixaban – dose will be defined after the results of the AUGUSTUS study (in which the standard doses for patients with non-valvular AF are used), dabigatran etexilate – 110 mg twice a day or 150 mg twice a day, rivaroxaban – 15 mg once a day (10 mg once a day in patients with creatinine clearance 30-49 mL/min), edoxaban – dose will be defined after the results of the ENTRUST-AF PCI study [5]. At the same time, it should be noted that for stroke prevention, the efficiency of the dose of rivaroxaban used in the PIONEER AF-PCI study (15 mg once a day) remains not fully studied due to the statistical limitations of this trial, at least comparing with the standard dose of VKA or rivaroxaban dose of 20 mg once a day in patients with normal creatinine clearance [6]. In case of combination of dabigatran and one antiplatelet agent (clopidogrel in this study), it is suggested to prefer the dose of 150 mg twice a day, leaving the dose of 110 mg twice a day for patients with elevated risk of bleeding.

Surgical interventions in patients taking NOAC

The data on optimal approaches for the use of NOAC in surgical interventions are limited. When deciding when to terminate and restart NOAC administration, one should consider patient's characteristics (age, history of bleeding, concomitant therapy, renal function) and operation-related factors (Table 2).

NOAC and restoration of sinus rhythm (cardioversion)

The possibilities of using NOAC in cardioversion are presented in the Figure 6.

NOAC and ischemic stroke

The details of treatment of acute ischemic stroke in patients taking NOAC are presented in the Figure 7.

Resuming NOAC therapy should be considered ≥1 day after transitory ischemic attack (TIA), ≥ 3 days after ischemic stroke with light neurologic deficit, ≥6-8 days after ischemic stroke with moderate neurologic deficit (in last two cases, it should be done after repeated CT or MRI during previous 24 h to exclude hemorrhagic transformation of ischemic stroke). Earlier start of NOAC therapy is suggested for patients with high risk of recurrent stroke (in particular, in case of left atrial appendage thrombus) without hemorrhagic transformation of ischemic stroke proved with the results of CT or MRI. These approaches correspond to the suggestions of other expert groups of the ESC.

NOAC after intracranial haemorrhage

It is recommended to consider the resumption of NOAC therapy 4-8 weeks after intracranial hemorrhage (after possible repeat of CT or MRI).

Arguments favouring refusal of NOAC therapy resumption:

- Severe intracranial hemorrhage;
- Multiple cerebral hemorrhages (in particular, > 10);
- Lack of reversible/treatable cause of bleeding;
- Elderly age;
- Bleeding during a break in taking anticoagulants;
- Bleeding occurred while taking adequate or reduced dose of NOAC;
- Uncontrollable arterial hypertension;
- Chronic alcohol abuse;
- The need for dual antiplatelet therapy after PCI.

In these cases, the possibility of the implantation of left atrial appendage occluder should be discussed.

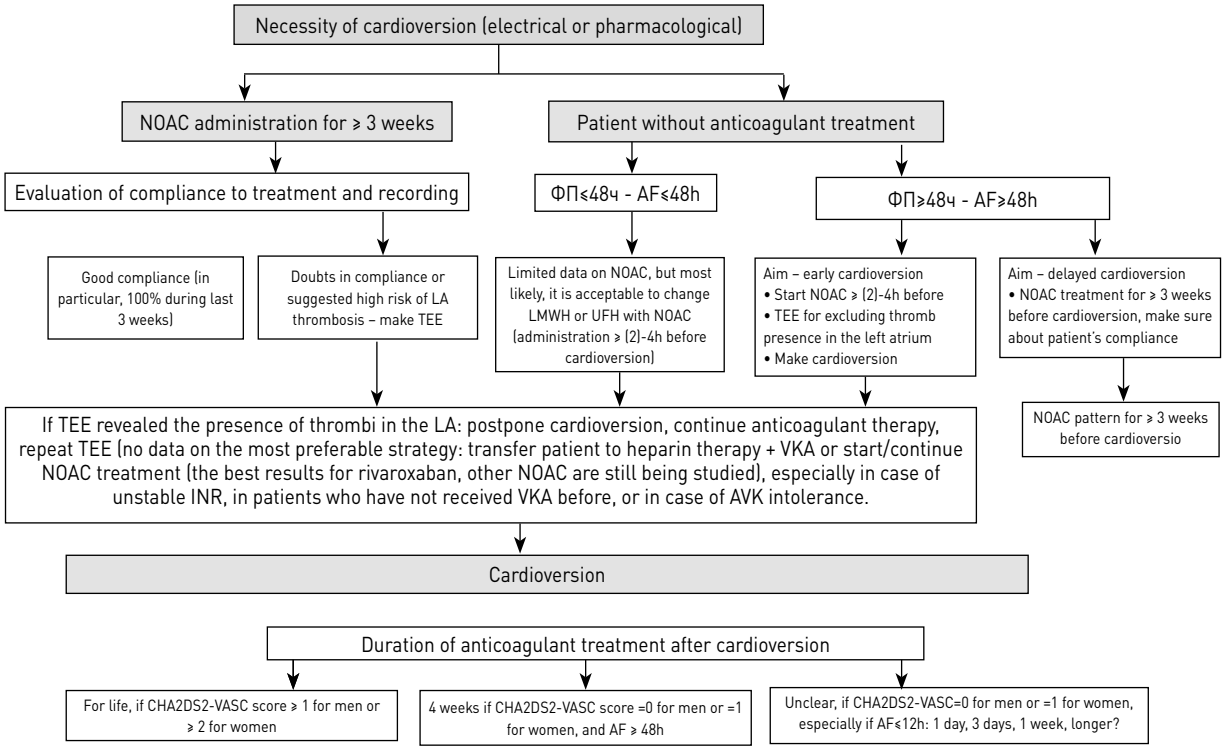
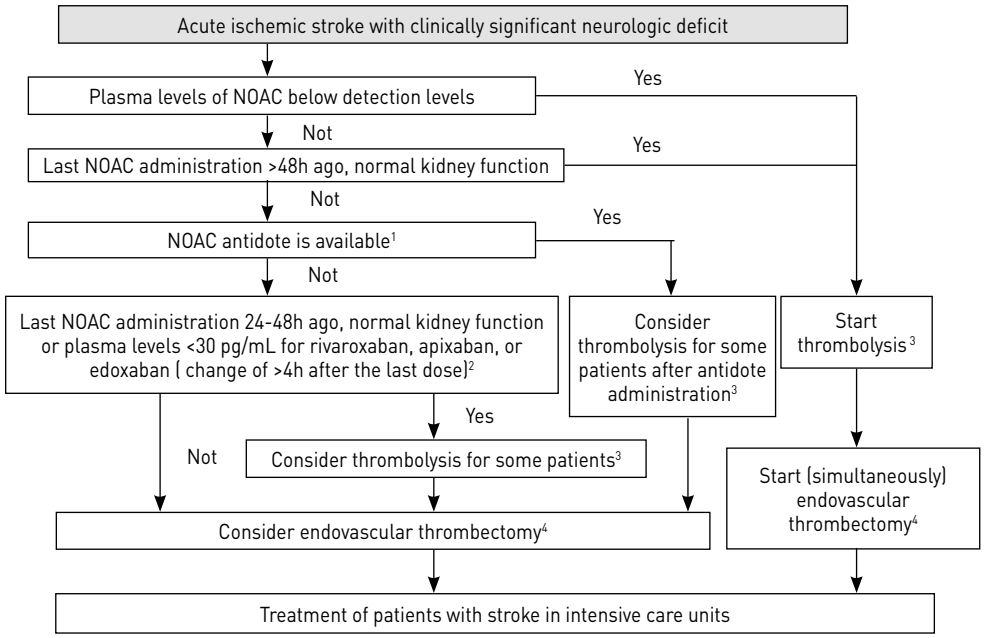


Figure 6. NOAC in cardioversion
Comments: LMWH – low molecular weight heparin, UFH – unfractionated heparin, TEE – transesophageal echocardiography, LA – left atrium.



Comments:
1 currently the antidote is available just for dabigatran (idarucizumab);
2 agreement of the experts;
3 in case of presence of necessary indications and absence of contraindications;
4 endovascular thrombectomy should be performed just in case of target vessel occlusion, presence of indications and acceptability of the procedure according to the existing evidences.

Figure 7. Treatment of acute ischemic stroke in patients taking NOAC

These approaches correspond to the suggestions of other expert groups of the ESC.

NOAC after gastrointestinal bleeding

It is recommended to consider the resumption of NOAC therapy 4-7 days after gastrointestinal bleeding. Arguments favouring refusal of NOAC therapy resumption:

- Undetected area of bleeding;
- Multiple angiodysplasia in the digestive tract;
- Lack of reversible/treatable cause of bleeding;
- Bleeding during a break in taking anticoagulants;
- Chronic alcohol abuse;
- The need for dual antiplatelet therapy after PCI;
- Elderly age.

In these cases, the possibility of the implantation of left atrial appendage occluder should be discussed.

Conflict of interests: None declared.

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International Heart and Vascular Disease Journal • Volume 6, № 19, September 2018
Journal of the Cardioprogress Foundation

Important results from ESC Congress 2018

Another annual Congress of the European Society of Cardiology (ESC) was held in Munich (Germany) on August 25-29, 2018. The ESC Congress ranks among the three most important and visited international cardiologic scientific events. More than 31 thousand delegates from 150 countries and 5 continents participated in this congress.

The President of the ESC Prof. Jeroen Bax presented the golden medal, the highest award of the ESC, to the President of the Russian Society of Cardiology academician Yevgeny Shlyakhto.

The scientific program of the ESC Congress was extensive and included more than 500 workshops and sessions attended by recognized international experts, clinical practitioners and young scientists from different countries. 400 topics of cardiology and related conditions have been observed during the Congress.

Hot Line sessions are the most followed scientific events of the ESC Congress and they are traditionally held in the main conference room (Munich Hall). This year results of new major trials in different areas of cardiology were discussed during five Hot Line and Late-Breaking Clinical Trials sessions. In particular the results of several long-awaited clinical studies were presented: **ARRIVE** (Aspirin to Reduce Risk of Initial Vascular Events), **ASCEND** Aspirin (A randomized trial of aspirin versus placebo for primary cardiovascular prevention in 15,480 people with diabetes), **ASCEND** (A randomized trial of omega-3 fatty acids (fish oil) versus placebo for primary cardiovascular prevention in 15,480 people with diabetes), **COMMANDER** HF (Randomized Study Comparing Rivaroxaban with Placebo in Subjects with Heart Failure and Significant Coronary Artery Disease Following an Episode of Decompensated Heart Failure), **GLOBAL LEADERS TRIAL** (A randomized comparison of 24 month ticagrelor and 1 month aspirin versus 12 month dual antiplatelet therapy followed by aspirin monotherapy), **PURE** (Association of dietary quality and risk of cardiovascular disease and mortality in more than 218,000 people from over 50 countries).

16 workshops were dedicated to the rapidly growing area of "Digital medicine" that attracted wide attention of participants.

The scientific program of this year included numerous joint workshops. 32 joint symposiums with international and national societies of Northern and Southern Africa, Asia, and other European medical societies were held during the Congress. 10 workshops were organized by the worldwide known cardiological journals (European Heart Journal, Circulation, The New England Journal of Medicine, JAMA, The Journal of the American College Cardiology).

Notably, 10 educational sessions dedicated to general questions of cardiology, emergency care, interventional cardiology, electrophysiology/ablation, medical statistics, clinical trials, and diagnostic algorithms were organized for young cardiologists.

Within the framework of the scientific program, several interventional procedures were broadcast in real-time mode from international educational centres of Italy, England, Germany, and Spain.

Scientific program of the Congress included satellite symposiums that involved international manufacturers of medicines and medical equipment.

Poster session was the important part of the scientific program. Poster presentations were divided into 9 directions and two formats: traditional posters and electronic posters.

The Conference book included more than 4500 abstracts, a part of them was selected for oral presentations.

According to the tradition, the Congress presented updated clinical guidelines:

- Guidelines on treatment of arterial hypertension;
- Guidelines on myocardial revascularization;
- The fourth universal definition of myocardial infarction;
- Guidelines on treatment of cardiovascular diseases during pregnancy;
- Guidelines on diagnostics and treatment of syncopal conditions.

New highlights in diagnostics and treatment of cardiovascular diseases were presented at exhibition supported by 200 manufacturers of pharmacological agents and medical equipment.

The leading Russian scientists were chosen as co-chairmen of different workshops and presented their results at oral and poster sessions. Several young Russian researchers received awards for their scientific work. The Russian Society of Cardiology participated in exhibition of national cardiological societies.

More detailed information on the ESC Congress can be found on its official website www.escardio.org.

The next ESC Congress will be held in Paris (France), on August 31- September 4, 2019.

International Heart and Vascular Disease
Journal • Volume 6, № 19, September 2018

Journal of the Cardioprogress Foundation

Author Guidelines

MANUSCRIPT PUBLICATION RULES IN THE INTERNATIONAL HEART AND VASCULAR DISEASE JOURNAL

Disclaimer: Edition of rules come into force since November, 2018. The rules describe the conditions of publication of manuscripts (articles) through the site http://www.heart-vdj.com. The editorial Board is ready to answer questions and help authors by e-mail: submissions.ihvdj@gmail.com.

The *International heart and vascular disease journal* has been published since 2013. It is official journal of the Cardioprogress Foundation. The target audience of this peer-reviewed journal is cardiologists and internal disease specialists. The journal is primarily focused on questions of epidemiology, prevention, and cardiac pharmacotherapy. It also publishes lectures and literature reviews on various problems of modern cardiology, reports on new diagnostic methods, and other information which is important for the practitioners.

The General criteria for the publication of articles in the International heart and vascular disease journal are the relevance, novelty of the material and its value in theoretical and/or applied aspects.

The languages of publications are Russian and English. Journal is peer-reviewed, with multistage editing. Editorial board is presented by the leading cardiologists from different countries and Russia.

International heart and vascular disease journal aims to ensure that its publications fulfill the requirements of international publishing standards, such as the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, by the International Committee of Medical Journal Editors, ICMJE (http://www.icmje.org), and the recommendations by the Committee on Publication Ethics, COPE (http://www.publicationethics.org.uk).

All clinical trials should be performed and described in full accordance with the CONSORT standards (http://www.consort-statement.org), observational research — STROBE (http://www.strobe-statement.org), systematic reviews and meta-analyses — PRISMA (http://www.prisma-statement.org), diagnostic accuracy — STAR (http://www.stard-statement.org).

I. The International heart and vascular disease journal accepts the following manuscripts:

1) *Original papers* present the results of clinical studies. The word limit is 3,000 (including references, tables, and figure legends). The maximal number of references is 15. The structured abstract should contain 5 sections (**Aim, Material and Methods, Results, Conclusion**, and **Key words**), and be no longer than 300 words.

2) *Lectures*, or clinically oriented reviews, are written by experts in broader areas of medicine. Lectures could be focused on epidemiology, pathophysiology, diagnostics, treatment, and prevention. The word limit is 5,000 (including references, tables, and figure legends). The maximal reference number is 80. The unstructured abstract is no longer than 150 words.

3) *Literature reviews* are focused on more specific topics, compared to lectures. The word limit is 4,500 (including references, tables, and figure legends). The maximal reference number is 50. The unstructured abstract is up to 150 words.

4) *Clinical case* is a brief report on a complex diagnostic problem and its solution, or a description of

a rare clinical observation. The word limit is 600 (including references, tables, and figure legends). The maximal number of references is 5. No abstract is required.

5) *Clinical opinion* informs the readers on the topics of cardiovascular medicine and related disciplines. The word limit is 2,500 (including references, tables, and figure legends). The maximal number of references is 15.

The journal accepts for publication original phase 2, 3 and 4 clinical studies. Literature reviews should be based on sources not older than 5 years.

II. Information about the article, which includes the following sections, is combined into a single file «letter (cover)»:

1) the manuscript is not under consideration in another edition; 2) has not been previously published; 3) contains a full disclosure of the conflict of interest; 4) all authors meet the criteria of authorship, it was read and approved; 5) the author (s) are responsible for the power of attorney submitted in the manuscript materials. 6) all contact information of the author responsible for correspondence; 7) information about previous publications of the authors on the same topic or pre-publication.

If the manuscript is a part of the thesis, it is necessary **to specify** the estimated terms of thesis defense.

The «letter of direction (accompanying)» should be made out on one or two sheets. Using the form of the official institution-at the choice of the author's team. In the address: «to The chief editor of the Russian cardiology journal, academician of RAS, Professor Oganov R. G.». The signatures of **all authors** should be placed at the bottom.

«Directional (cover) letter» is scanned. File format. jpeg attached as an additional file of the manuscript.

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III. Registration on the Website and information about the authors.

1. **Any of the authors can submit an article to the journal.** Usually it is the one who then conducts correspondence with the editorial office and to whose mail notification letters come (when submitting a manuscript through the site, you can choose to send notifications to all authors).

The author registers on the site, entering his full name. In the form to be filled in when submitting an article, all authors and all additional information (places of work, positions, academic titles, institutions, ORCID — all authors) are indicated.

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Example of design:

THE PREVALENCE OF RISK FACTORS OF NONCOMMUNICABLE DISEASES IN THE RUSSIAN POPULATION IN 2012–2013. THE RESEARCH RESULTS OF THE ESSE-RF

Muromtseva G. A. [1], Kontsevaya A.V. [1], Konstantinov V. V. [1], Artamonova G. V. [2], Galaganova T. M. [3],...

[1] FGBU State research center of preventive medicine of the Ministry of health of Russia, Moscow;

[2] FGBU Research Institute of complex problems of cardiovascular diseases SB RAMS, Kemerovo;

[3] RD VPO North Ossetian state medical Academy, Vladikavkaz;..., Russia.

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The article title is written in capital letters (PREVALENCE of RISK FACTORS...), the end point is not needed. The title should clearly reflect the purpose of the work.

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Abbreviations should be generally accepted and understandable to the reader, in accordance with the generally accepted norms in the scientific literature. Undesirable abbreviations that coincide in writing with others that have a different meaning.

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Tables should contain the compressed, necessary data. Each table is placed at the end of the text (after the list of references) with the number, name and explanation (note, abbreviations).

The tables should clearly indicate the dimension of the indicators and the form of data (M±m; M±SD; Me; Mo; percentiles, etc.). All figures, totals and percentages should be carefully verified, and also correspond to the mention in the text. The explanatory notes are given below the table, if necessary. The footnotes must be in the following order: *, †, §, ||, ¶, #, **, †† etc.

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Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger; 1990. p.398–420. ISBN 0000–0000.

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6. The editorial Board informs the Author of the results of the review by e-mail.

7. If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

8. If the reviewer makes a conclusion about the possibility of publication of the article and gives instructions on the need for its correction, the Editorial Board sends the review to the Author with a proposal to take into account the recommendations of the reviewer in the preparation of a new version of the article or to refute them. In this case, the Author needs to make changes to the last version of the article file, which is located on the site (download file from the site, make changes and place the corrected article again, after removing the primary (uncorrected) version). The revised article is re-sent for review, and the conclusion is given that all the recommendations of the reviewer were taken into account. After receiving a positive response of the reviewer, the article is given to the expert on statistics and after a positive report is accepted for further work.

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XIII. Journal subscription

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XIV. Journal subscription

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http://www.heart-vdj.com

On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

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