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Central directions for reducing cardiovascular mortality: what can be changed today?

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The article provides modern data on the prevalence of cardiovascular diseases and mortality in Europe and Russia. Groups of high-risk patients requiring special attention when conducting measures to reduce cardiovascular mortality are discussed: patients with hypertension, including resistant, patients with severe dyslipidemia, heart failure, and atrial fibrillation. Particular attention is paid to the problem of effective and safe treatment and reducing cardiovascular mortality in patients with atrial fibrillation and a high risk of stroke. The treatment of these patients may be most successful due to the availability of effective medications that reduce cardiovascular mortality. The article outlines the major paradigms of modern healthcare: focus on results and patient, integration of inpatient and outpatient health care units and accelerating the innovation in the diagnosis and treatment of patients with cardiovascular diseases.

Key words: cardiovascular mortality, resistant hypertension, dyslipidemia, atrial fibrillation, anticoagulants.

Relationships and Activities: none.

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Cardiovascular disease (CVD) is the leading cause of death worldwide. Every year 17,5 million people die due to CVD, and most of these deaths are potentially preventable [1]. In 2020, data on CVD statistics were published in 52 European Society of Cardiology (ESC) member countries [2]. In these countries, in 2018, 2,2 million women and 1,9 million men died from cardiovascular diseases, while cardiovascular mortality (CVM) was 47% of all causes in women and 39% — in men [2]. In CVM structure, the first place in women and men is coronary artery disease (CAD) (18% and 17%, respectively), and the second place is stroke (12% and 8%, respectively) [2]. In middle per capita income countries, including the Russian Federation, the proportion of CVM is higher than in countries with high-income economies [2].

Using the methods of statistical analysis, it was proved that in the countries united by the ESC, the potential years of life lost (PYLLs) due CVD in 2017 was 28 million for women and 38 million for men, which accounts for 37% of PYLLs for women and 34% of PYLLs for men [2]. CVD are more responsible for PYLLs in European countries with a middle per capita income than in high-income countries, both among women (43% and 28%, respectively) and among men (39% and 28%, respectively) [2].

In Russia, CVM is associated with every second death and exceeds CVM in Europe and the United States [3-5]. According to the Russian Federal State Statistics Service, 841915 people died due to CVD in 2018 [3]. At the same time, in recent years there has been favorable dynamics — in the period from 2005 to 2018 the CVM decreased by 36,6% [3, 4], and in the period from 2000 to 2018 the proportion of CVD in the structure of all-cause mortality decreased from 55,3 to 46,3% [4]. In addition, death is one of the most reliably ascertained outcomes in most European countries [2]. In Russia, one of the priority tasks is to increase life expectancy to 78 years by 2024 [6] and to reduce CVM to <450 cases per 100 thousand population by 2024, that is, by 21,5% over the next 5 years [7].

In 2013, the World Health Organization (WHO) announced a strategy to reduce mortality due to CVD, diabetes, cancer and chronic lung diseases by 25% by 2025 compared to 2010 [1]. By 2019, mortality in high-income European countries has decreased by 9% for women and 11% for men, while in countries with middle-income economies it has decreased by 8% for women and only 2% for men [2].

In Russia, the decrease in CVM in recent decades is largely associated with the reorganization of cardiology care, the creation of regional vascular centers, the introduction of highly effective interventional treatment of acute coronary syndrome, surgery of heart defects, interventional treatment of arrhythmias and prevention of sudden cardiac death. At the same time, only high-tech methods of treatment cannot completely solve the problem of reducing CVM. The modulation of cardiovascular risk factors (CVR), primary and secondary prevention of CVD, increasing medication adherence of patients, including after the use of high-tech methods, are also of great importance for reducing mortality. It is also important to develop pharmacology and create new drug classes. Some of these drugs affect not only hypertension (HTN), hyperlipidemia, hyperglycemia, the course of CAD, heart failure (HF), but also affect hard endpoints, including all-cause and CVM. So, it is necessary to determine the main directions for reducing CVM.

High-risk patient groups requiring special attention

Target groups of high-risk patients should be identified that require special attention and active measures to reduce mortality. These high-risk groups include patients with severe dyslipidemia, resistant HTN, HF, and atrial fibrillation (AF).

Dyslipidemia

Severe dyslipidemia is one of the modifiable risk factors for CVD and mortality. Prospective randomized clinical trials (RCT) have demonstrated that elevated levels of atherogenic lipids, including low-density lipoprotein cholesterol (LDL-C), increase the risk of atherosclerosis-related CVD [8]. One of the serious problems of modern medicine is insufficient detection of dyslipidemia for primary and secondary prevention of CVD, including in high-risk patients with type 2 diabetes, stroke, and peripheral artery disease.

There is no doubt that treatment of dyslipidemia reduces CVR. Meta-analysis of the Cholesterol Treatment Trialists' Collaboration, which included data on more than 170000 patients from 26 RCT, proved that a decrease in LDL-C by 1 mmol/L over 5 years was associated with a decrease in major vascular events by 22%, major coronary events by 23%, stroke by 17% and all-cause mortality by 10% [9]. Secondary prevention with statins reduces the risk of recurrent stroke by 12% with a decrease in LDL-C by 1 mmol/L and decreases CVM [10]. The low statin prescription rate leads to non-achievement of the lipid target level and to an increased risk of myocardial infarction (MI), stroke and premature death [11]. According to the ARGO study, in 2013-2014, hypercholesterolemia was detected in 81,3% of women and 78,9% of men [12]. Among patients with CAD, HTN, revascularization, a history of ischemic stroke or peripheral artery disease, only 43% received statin therapy, and 27,2% and 9,1% of patients received high-dose atorvastatin and

rosuvastatin therapy, respectively. At the same time, only 2,04% of patients with CAD and 7,38% of patients with a history of MI and surgical or percutaneous coronary intervention reached the target LDL-C level [12].

In patients with high CVR, ESC/EAS Guidelines for the management of dyslipidemias (2019) recommend a decrease in LDL-C by 50% or more and achieving a target level of <1,8 mmol/L, and in very high-risk patients — <1,4 mmol/L [8]. This level of atherogenic lipids is extremely difficult to achieve with statin monotherapy.

Combined lipid-lowering therapy more effectively reduces the lipid levels. According to the REDUCE-IT study, therapy with combination of statins and ezetimibe reduces the incidence of composite endpoint, including cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization and unstable angina by 25% over 4,9 years of therapy [13].

According to FOURIER study, therapy with a combination of statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) evolocumab in patients with atherosclerotic CVD not only effectively reduces the LDL-C levels during long-term treatment, but also reduces the risk of primary endpoint, including cardiovascular death, MI, stroke, hospitalization due to unstable angina or coronary revascularization by 15% [14]. At the same time, combination therapy for dyslipidemia is not used often enough due to the rigidity of physicians, low medication adherence of patients, the high cost of some drugs and, to a lesser extent, due to adverse events.

Resistant hypertension

The problem of treating HTN patients remains relevant. According to the ESSE-RF study, only 16,4% of men and 32,6% of women with essential HTN had a target blood pressure level [15]. Resistant HTN is observed in 17,7% of hypertensive patients [16]. According to a scientific statement from the American Heart Association (2018), resistant HTN increases the risk of stroke by 14%, MI by 24% and the risk of death by 6% [17]. Treatment of patients with resistant HTN is a complex problem that requires excluding the secondary HTN, treating comorbidities, stopping alcohol consumption, limiting the intake of non-steroidal anti-inflammatory drugs, increasing low physical activity and treating obstructive sleep apnea. In the treatment of hypertensive patients, it is necessary to increase the non-medication and medication adherence of patients. Drug treatment of patients with resistant HTN includes 4 or more antihypertensive drugs, including renin-angiotensin-aldosterone system inhibitors, calcium channels blockers and thiazide diuretics (chlorthalidone is preferred), and in case of insufficient effectiveness — mineralocorticoid receptor antagonists [18]. The PATHWAY-2 study proved that spironolactone is more effective in patients with resistant HTN than bisoprolol or doxazosin [19]. In case of insufficient effectiveness of therapy in patients with CAD or HF, beta-blockers should be added, and in patients without mentioned diseases — central alpha-adrenergic agonists (clonidine, methyldopa) or peripheral vasodilators (hydralazine) [18, 20]. Analysis of the SPRINT and ACCORD studies showed that the optimal systolic blood pressure to reduce incidence of adverse outcomes such as MI, stroke, HF, CVM and all-cause mortality in patients with/without resistant HTN is <120 mm Hg [21]. A serious problem in the treatment of resistant HTN is the low medication adherence of patients, which reaches only 31,2% [22]. ESC (2018) and ACC/AHA (2017) guidelines do not recommend the routine use of devices for the treatment of resistant HTN [23, 24]. Consequently, the problem of resistant HTN treatment cannot be considered solved at present. The number of hypertensive patients, including those with resistant HTN, can be significantly reduced through prevention and a healthy lifestyle.

Heart failure

HF is one of the most relevant problems of modern cardiology [25]. The prevalence of HF in developed countries among the adult population is 1-2%, progressively increasing with age [26]. There are currently 15 million HF patients in Europe [27]. The absolute number of patients with end-stage HF is increasing due to life expectancy increase and due to the improvement of methods of treating cardiovascular patients. The presence of HF increases the mortality rate by 7-17% per year [25].

Over the past 30 years, there were progressive changes in the treatment of HF patients that have increased the survival of those with HF with reduced ejection fraction (HFrEF) [25]. Neurohumoral antagonists (angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor blockers (ARBs), mineralocorticoid receptor antagonists and beta-blockers) are recommended for all patients with HFrEF due to reducing mortality [25]. In recent years, new drugs have introduced: sacubitril/valsartan, ivabradine, sodium-glucose co-transporter-2 inhibitors. Sacubitril/valsartan is recommended for patients with HFrEF if HF symptoms maintain during therapy with ACE inhibitors/ARBs, since it is more effective than enalapril in reducing mortality and CVM [28]. Ivabradine reduces the composite endpoint — mortality or hospitalization due to HF in symptomatic patients with HFrEF and sinus rhythm ⩾70 [29].

According to EMPA-REG OUTCOME study, sodium-glucose co-transporter-2 inhibitor empagliflozin in patients with type 2 diabetes decreased the composite primary endpoint 3P-MACE (cardiovascular death, non-fatal MI, non-fatal stroke) by 14%, reduced the risk of hospitalization due to HF by 35%, reduced all-cause mortality by 32% and CVM by 38% [30].

Despite significant progress in the treatment of patients with HF, in actual clinical practice, patients with HF are often treated inadequately, which leads to unfavorable outcomes. Often, titration of ACE inhibitors/ARBs, beta-blockers and diuretics is not carried out, and drugs with verified effect on reducing mortality (sacubitril/valsartan, empagliflozin) are not prescribed [28, 30]. The main reasons for inadequate treatment of outpatients are changes in therapy regimens and ineffective hemodynamic monitoring. According to the EPOHA-D-CHF study, changes in treatment regimen after decompensated HF were carried out in 78,5% of patients within a year [31].

Atrial fibrillation

Prevalence of AF in Europe is 1-2% [32]. Mortality in patients with AF is higher 1,5-2 times [27]. The increase in mortality is due to the high incidence of stroke in AF patients, since this arrhythmia is one of the most important risk factors for stroke [32]. The number of stroke patients in ESC member countries in 2017 amounted to 20,4 million, and stroke was more common among residents of Eastern Europe and in countries with a low per capita income [2]. The age-standardized stroke prevalence in the Russian Federation in women is 1700 and more, and in men 1600-1900 per 100 thousand population [2]. Stroke prevention is one of the priorities in reducing CVM.

In 2017, in 54 ESC member countries, 10000000 AF patients were recorded; the average age-standardized AF prevalence in these countries was 571,8, and in Russia — 474 in women and 732 in men per 100 thousand population [2]. It is assumed that the number of patients with AF by 2060 will doubled (compared to 2010) and reach 17900000 patients, and AF will be observed in 1 in 4 people over 40 years of age [33, 34].

Attention should be paid to the fact that AF is often not diagnosed due to asymptomatic course or rare and short paroxysms, which does not allow registering arrhythmias. The incidence of asymptomatic AF in clinical trials varies from 1,4% to 34,8%, depending on the diagnosis method — most often AF was detected by implanted devices [35]. Asymptomatic AF significantly increases the risk of stroke and systemic embolism [36]. The ASSERT study, which included hypertensive patients over 65 years of age with an implanted dual-chamber pacemaker or cardioverter-defibrillator, showed that asymptomatic AF developed in 18,8% of patients during a mean follow-up period of 2,5 years. The risk of stroke and embolism was 3 times higher in patients with asymptomatic AF lasting more than 24 hours compared with those without AF [36]. The US study found that AF was not diagnosed in 18% of people with AF. At the same time, of particular importance is the fact that 77% of them have a $CHADS_2$ score of ⩾1, and 56% — ⩾2, that is, most have a high risk of stroke and, therefore, indications for anticoagulant therapy [37]. According to the CRISTAL-AF study, the detection rate of AF after cryptogenic stroke in patients with an implanted cardiac monitor is 14 times higher [38]. Therefore, in patients with stroke of undetermined source, electrocardiogram monitoring (at least 72 hours) should be performed in order to diagnose AF for prescribing anticoagulants for the secondary prevention of stroke. New devices are increasingly being used to diagnose AF: an Apple Watch, a BP monitor with AF detection (WatchBP Home A, Microlife), smartphones, and patch-monitors [35]. The fact that new devices and methods for AF diagnosis are being created indicates that the AF diagnosis is extremely important, since it completely changes the management strategy.

One of the main areas of therapy for patients with AF is the prevention of stroke and systemic embolism using anticoagulant therapy [32]. Anticoagulation is specified by the risk of stroke and significantly reduces the risk of thromboembolic events and death in patients with AF [32]. At the same time, according to the Risk-Stroke register, out of 94000 people with ischemic stroke, 22% were previously diagnosed with AF, but only 16% of them received anticoagulant therapy within 6 months before stroke [39]. Vitamin K antagonists effectively reduce the risk of thromboembolic events in patients with AF [40]. Well-managed warfarin therapy is associated with a 64% reduction in stroke risk and a 26% reduction in mortality compared with placebo [41], but is also associated with an increased risk of major bleeding [40]. In addition, the use of warfarin is associated with a need for laboratory monitoring, interaction with other drugs and food products, difficulties in dose selection and long-tern maintaining an optimal anticoagulant effect [42]. For effective warfarin treatment, the time in therapeutic range of international normalized ratio (INR) of 2,0 to 3,0 must be >70%. Practically, achieving such an effect is extremely difficult. In RCT, the time of therapeutic range for warfarin ranged from 55% to 66% [43-45]. In actual clinical

practice, the results of monitoring the effectiveness of warfarin therapy are usually lower. According to cohort study by E. I. Baranova et al., only 40% of patients with AF and indications for anticoagulation received these drugs, and INR within the target range was recorded only in 26,8 patients [46]. According to the analysis of anticoagulant therapy in AF patients in several Russian cities, the achievement of the target INR does not exceed 40% [47]. The efficacy and safety of direct oral anticoagulants (DOAC) has been compared with warfarin in large RCTs, including >150000 patients [48]. DOAC in RCTs and in actual clinical practice have shown no less efficacy and, undoubtedly, higher safety compared with vitamin K antagonists [49-52]. At the same time, the frequency of hemorrhagic strokes and intracranial bleeding with the use of DOAC is significantly lower in comparison with warfarin, and dabigatran etexilate is associated with a reduction in the risk of ischemic stroke by 24% [49, 53].

It should be also noted that RCTs demonstrated that long-term use of dabigatran etexilate and apixaban reduce the risk of all-cause mortality [51, 54, 55]. Of all DOACs, only dabigatran at a dose of 150 mg 2 times/day showed a significant decrease in CVM compared with well-managed warfarin with a relative risk of 0,85 (95% confidence interval 0,72-0,99), p=0,0430 [49, 53].

Despite these positive effects of DOAC, many patients with AF still do not receive effective antithrombotic therapy, although, the dynamics of anticoagulant prescription rate is undoubtedly positive. In particular, the GLORIA-AF registry demonstrated that the majority of patients with AF and a high risk of stroke on all continents receive anticoagulants, but the proportion of patients who do not receive antithrombotic therapy or receive only antiplatelet drugs varies widely depending on age and continents [52]. According to the GLORIA-AF registry, the most unfavorable situation with anticoagulant prescription in Asian countries. In particular, 41,8% of patients aged 65-74 years and 45,9% of patients 85 years and older did not receive adequate antithrombotic therapy [52]. According to the Russian cohort study with AF outpatients, anticoagulant therapy (if indicated) was not prescribed in 25,7% of patients. At the same time, 13,4% of patients after stroke or transient ischemic attack also did not receive anticoagulants [56].

Anticoagulant therapy in patients with AF, a high risk of stroke, and withoyt contraindications, should be carried out for life, since this affects the prognosis of patients with AF. At present, it is of particular importance to anticoagulant withdrawal in outpatients by a physician or by themselves. Discontinuation of anticoagulant therapy increases the risk of stroke in patients with AF by 4,21 times, and the risk of death by 3,43 times [57]. Anticoagulant withdrawal is often due to the risk of major bleeding. However, the incidence of hemorrhagic strokes and intracranial bleeding with the use of DOAC is significantly lower than with warfarin [49-51]. When DOACs is prescribed in accordance with the European guidelines, the incidence of major bleeding in RCTs with the dabigatran and apixaban is lower than with warfarin, and the number of major gastrointestinal bleeding is comparable [51, 54]. During treatment with rivaroxaban versus warfarin, the incidence of major bleeding was comparable, and the risk of major gastrointestinal bleeding was higher [50]. In actual clinical practice, a similar data is observed — in a national cohort study with 52476 patients with AF who were first prescribed DOAC, major bleeding was observed less frequently with dabigatran than rivaroxaban, and there were no differences in the frequency of bleeding between dabigatran and apixaban [58].

The safety of DOAC therapy has increased in recent years, since there are drugs for the reversal of anticoagulant effects in clinical practice, which are used for life-threatening bleeding. According to statistics, 3,5% of patients per year need urgent reversal of the anticoagulant effect [59]. It should be emphasized that the need to stop the anticoagulant action arises not only with massive bleeding or internal bleeding into a vital organ (1,5% per year), but also when emergency surgery or procedure with a high risk of bleeding is necessary (2% per year) [59]. Only dabigatran etexilate has a drug designed for the reversal of its anticoagulant effects — idarucizumab, and it is registered in the Russian Federation [60]. The ability to quickly reverse the anticoagulant effect increases the confidence of physicians and patients and, therefore, leads to an increase in the number of patients taking anticoagulants, and as a result, to a decrease in the incidence of strokes and CVM [61].

Thus, this data on the diagnosis and treatment of AF aimed at preventing stroke and systemic embolism is an example of how the high-precision available methods of early diagnosis, highly effective treatment and prevention of thromboembolic events can actually reduce CVM.

The major paradigms of modern healthcare:

1. Focus on effects and results;
2. Patient-centered care: the interests of a patient are more significant than of an institution, a system, and medical workers;
3. Process integration: continuity between in- and outpatient specialists;

4. Accelerating the innovation introduction: overcoming bureaucratic obstacles for the practical implementation of new effective technologies.

There are many challenges of modern medicine, first of all, it is patient-centered care aimed at increasing the patient's life expectancy and quality of life.

There are following key areas of modern cardiology:

1. Early diagnosis of diseases, the treatment of which can affect the prognosis and quality of life of a patient.

2. Primary and secondary prevention and treatment using modern technologies aimed at increasing the physicians' education, patient awareness, and medication adherence.

3. Setting up a task to create treatment methods that ensure high efficiency and safety of therapy, which can lead to a decrease in CVM.

The strategy for monitoring and managing risks in cardiology consists of primary prevention, early treatment, treatment of an acute event, secondary prevention, and treatment of complications. This strategy is aimed at reducing CVM, which is one of the priority tasks of Russian healthcare system [7].

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