MODERN VIEW ON CHRONIC HEART FAILURE AND ITS TREATMENT

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Annotation. The article presents the modern definition and classification of chronic heart failure, as well as the main reasons leading to its development. Diagnostic methods, methods of pharmacological and non-drug treatment of chronic heart failure, recommended by clinical guidelines, are presented in a concise form.

Key words: chronic heart failure, left ventricular dysfunction, pharmacotherapy.

Basic concepts . Chronic heart failure (CHF) is a clinical syndrome in which patients have typical complaints (shortness of breath, decreased exercise tolerance, fatigue) and objective signs (crackles in the lungs, hepatomegaly , dilatation of the jugular veins) caused by a violation of the structure and function of the heart (primarily the left ventricle (LV)), which leads to a decrease in cardiac output and an increase in intracardiac pressure at rest or during exercise. Evidence of LV dysfunction is the most important argument for moving from a clinical hypothesis to a confirmed diagnosis [1, 2].

Chronic heart failure is not an independent disease, it is a complication, the outcome of cardiac diseases that disrupt the anatomy and function of the heart. Therefore, an important task facing a doctor who suspects or diagnoses CHF in a patient is to determine its cause. Although treatment for CHF syndrome is universal, the impact on its cause can vary significantly. Patients with CHF of ischemic etiology require pharmacotherapy aimed at eliminating the symptoms of coronary heart disease (CHD) (antianginal drugs) and improving the prognosis (statins , antiplatelet agents , angiotensin-converting enzyme inhibitors (ACEIs)), and surgical revascularization ; patients with arterial hypertension (AH) require antihypertensive drugs (including the possible use of calcium antagonists); if the symptoms of heart failure are due to tachyarrhythmias , treatment aimed at reducing the frequency of the ventricular response or electrical cardioversion is necessary . Congenital and acquired heart defects stand apart, since once they are detected, the symptoms of heart failure cannot be eliminated other than through surgery, for example, valve replacement.

Modern diagnostic methods (primarily echocardiography (EchoCG)) make it possible to identify two main variants of LV dysfunction in patients with CHF: in the first case, its contractile, systolic function is predominantly affected, in the second - diastolic, the ability to relax. In the first case, a significant decrease in the ejection fraction (EF) of the LV (<40%) is determined due to a local or diffuse violation of its contractility; often dilatation of the cavity and thinning of the walls of the LV indicate

CHF with reduced or low EF (CHF- rEF). In the second case, EF remains normal, preserved (>50%), local contractility disorders are uncharacteristic, LV volume may be normal or even decrease, wall thickness is usually increased, using special techniques (Doppler study of transmitral blood flow or tissue Doppler) a violation is detected LV diastolic function (CHF with preserved EF (CHF- pEF)). Recently, a subgroup of patients with CHF has been identified whose EF is 40–49%, but so far this has little impact on practical decision-making.

Classification of CHF

Classification of CHF created by N.D. Strazhesko and V.Kh. Vasilenko, describes the progression of hemodynamic disorders in the systemic and pulmonary circulation and manifestations of CHF during its existence, therefore, the stage of CHF can only increase.

Classification of CHF developed by NYHA (New York Heart Association - New York Heart Association), is based on an assessment of the severity of functional limitations. During the conversation, the doctor finds out from the patient to what extent the symptoms of CHF limit his daily activity. Functional class (FC) can improve, for example, under the influence of proper treatment. The diagnosis must include both the stage and FC of CHF, since both classifications significantly complement each other.

Etiology of CHF

The main reasons for the development of CHF include: arterial hypertension (95.5%), coronary heart disease (69.7%), previous myocardial infarction (15.3%), diabetes mellitus (15.9%). A combination of coronary heart disease and arterial hypertension occurs in most patients with CHF. COPD (chronic obstructive pulmonary disease) accounts for 13% of all causes of CHF, chronic and paroxysmal atrial fibrillation - 12.8%, acute cerebrovascular accident - 10.3%.

Pathogenesis . CHF is a complex cascade of neurohumoral, hemodynamic and immunological reactions. The triggering factor in the pathogenesis of CHF is a drop in cardiac output and the development of hypoperfusion of organs and tissues. In response to a decrease in cardiac output, a number of neuroendocrine systems are activated, aimed at adapting the heart to hemodynamic overload and maintaining blood flow. With diastolic myocardial dysfunction, despite the preservation of cardiac output, ventricular relaxation slows down and the diastolic component is redistributed in favor of the atrial component (i.e., a significant part of the diastolic blood flow in the heart occurs not during the rapid filling phase, as is normal, but during active systole atria). These changes contribute to an increase in atrial pressure and size, increasing the risk of venous congestion in the pulmonary or systemic circulation, which is accompanied by clinical signs of HF, despite normal ventricular ejection fraction. With diastolic

dysfunction, the end result of the activation of compensatory mechanisms is an increase in ventricular filling pressure, which ensures sufficient diastolic blood flow to the heart.

The main systems involved in the pathogenesis of CHF are:

- activation of the sympathetic-adrenal system (SAS) and an increase in the concentration of catecholamines as one of the earliest compensatory factors in the occurrence of systolic or diastolic HF;
- activation of the renin– angiotensin – aldosterone system (RAAS) (circulating and tissue);
- the atrial natriuretic peptide system (ANUP) is a unique antagonist of the body's vasoconstrictor systems (ASC, RAAS, ADH and others) , causing vasodilating , natriuretic and diuretic effects, inhibiting the secretion of renin and aldosterone. This is one of the earliest compensatory mechanisms that prevents excessive vasoconstriction , Na + and water retention in the body, as well as an increase in pre- and afterload . However, despite the high level of circulating PNUP, the degree of its positive effects in CHF is markedly reduced, which is probably due to a decrease in receptor sensitivity and an increase in peptide cleavage.
- increased secretion of antidiuretic hormone (ADH) ;
- endothelial dysfunction - characterized by a predominance of vasoconstrictor endothelium-dependent influences (endothelin-1, thromboxane A2, prostaglandin PGH2, angiotensin II, etc.) and a natural increase in the tone of the vascular wall, acceleration of platelet aggregation and the processes of parietal thrombus formation , fibrosis and hypertrophy of cardiomyocytes .

However, subsequently, almost all compensatory mechanisms are transformed into pathogenetic factors that contribute to even greater disruption of the systolic and diastolic function of the heart and the formation of significant changes in hemodynamics characteristic of CHF.

Diagnostics

A clinical hypothesis about the presence of CHF in a patient is formulated by identifying characteristic complaints and objective signs. Since they are all low specific , differential diagnosis of shortness of breath, edema, weakness, hepatomegaly , etc. can cause difficulties. Collection of anamnesis should be aimed at identifying the disease causing CHF. Subsequently, the examination algorithm is structured in such a way as to identify LV dysfunction, determine its cause, and exclude alternative explanations for the patient's symptoms.

There are no specific manifestations of CHF on the electrocardiogram (ECG), but a normal ECG is observed quite rarely in patients with CHF. This method allows us to suggest the etiology of CHF, since most diseases leading to its development cause

changes in the ECG (signs of LV hypertrophy, scar changes, rhythm and conduction disturbances). X-ray of the chest organs allows you to evaluate the configuration of the heart and vascular bundle, identify cardiomegaly , signs of stagnation in the pulmonary circulation, hydrothorax. In addition, a radiograph of a patient with shortness of breath allows us to exclude other causes, focal changes, and changes in the mediastinum.

The most widespread, non-invasive and relatively cheap method of verifying CHF is echocardiography , which allows you to study the size and volume of the LV and right ventricle, left atrium, the thickness of the walls of the heart, quantify the systolic and/or diastolic function of the LV, study the functioning of the valve apparatus, and exclude rare causes of CHF (tumors, congenital defects, restrictive processes that disrupt the functioning of the LV due to external compression or increased endocardial rigidity).

The results of echocardiography in most cases allow us to formulate an initial diagnosis and develop a treatment plan. Other diagnostic tests are required when the diagnosis remains unclear (eg, poor imaging on echocardiography).

Transesophageal Echocardiography may be useful in patients with suspected aortic, valvular pathology, endocarditis, or congenital heart disease. In addition, this method allows us to exclude intracavitary thrombi, which often cannot be visualized during a conventional transthoracic examination. This must be done in patients with atrial fibrillation (AF) lasting more than 48 hours to make a decision about the possibility of cardioversion .

As a diagnostic test, especially if echocardiography is not available , determination of laboratory parameters reflecting the concentration of brain natriuretic peptide (BNP) in the blood can be used. These neurohumoral mediators increase renal sodium and water excretion, cause vasodilation , and are secreted by the myocardium in response to increased LV pre- or afterload . However, there are many factors that cause an increase in the level of BNP (old age, chronic disease and/or acute kidney injury, AF, hypertension, pulmonary embolism), which significantly reduces the diagnostic value of this indicator. Therefore, determining the level of BNP can be used to exclude, and not to establish a diagnosis of CHF: with normal or low values, the diagnosis of CHF can be considered excluded, and if they increase, the initial “working” diagnosis of CHF should still be confirmed using echocardiography . The test is of great relevance for confirming CHF in patients with characteristic symptoms and preserved LVEF.

Magnetic resonance imaging of the heart allows achieve high image quality and accurate assessment of parameters in patients with poor visualization during echocardiography . Magnetic resonance imaging is the method of choice for diagnosing congenital heart defects, amyloidosis, myocarditis, Fabry disease, and unclassified cardiomyopathies . Contrast magnetic resonance imaging helps to differentiate

ischemic and non-ischemic causes of CHF, as it allows to identify fibrosis/sclerosis. Compared to echocardiography, this method is less accessible and more expensive. Magnetic resonance imaging is not performed on patients with metal structures (joint prostheses, mechanical valves, pacemakers).

Computed tomography of the heart is used to

non-invasive imaging of the coronary arteries in patients with CHF and suspected coronary artery disease. However, coronary angiography is a more sensitive and specific method for diagnosing atherosclerosis of the coronary arteries, allowing, if necessary, to immediately proceed to therapeutic action.

Treatment of CHF

The goals of treating patients with diagnosed CHF are considered to be to improve the quality of life (by reducing the severity of clinical symptoms and functional limitations) and improve the prognosis (preventing or reducing the number of hospitalizations, reducing mortality and the incidence of cardiovascular complications) of patients. The success of the first task is usually obvious to the doctor and the patient, while the impact on

the prognosis of a particular patient cannot be assessed directly by the attending physician. We rely on data from large clinical trials that have shown improved survival of patients with CHF using certain approaches. Basically, such studies included patients with CHF- rEF , for whom a clear treatment algorithm was developed.

Pharmacotherapy of CHF- rEF (systolic)

Since our ability to influence the cause of CHF (systolic or diastolic dysfunction of the LV) is quite modest, a key way to improve the prognosis of patients is to suppress neurohumoral hyperactivation that occurs in response to impaired LV function. Reducing the activity of the renin- angiotensinaldosterone system (RAAS) with the help of ACEIs or angiotensin II receptor antagonists (ARAII), mineralocorticoid receptor antagonists (MCRA), and the sympathoadrenal system with the help of β-adrenergic blockers (BABs) made it possible to radically reduce the mortality of patients with CHF. Therefore, drugs from these groups, in the absence of contraindications or intolerance, should be recommended to all patients with CHF.

Correct use of ACE inhibitors involves titrating their dose from the minimum to the maximum tolerated. Careful monitoring of the patient's well-being, basic hemodynamic (blood pressure (BP) and heart rate (HR)) and laboratory (potassium and creatinine levels) parameters is necessary. Titration of the dose to the maximum is possible subject to several rules: initiation of therapy after compensation of CHF is achieved, while taking a pre-titrated dose of a diuretic (if indicated), the patient must have a stable body weight and normal concentration of electrolytes, drugs are

prescribed only to patients with a confirmed diagnosis and an understandable cause of CHF, the titration step is usually 5–7 days, longer in elderly and severe patients. Long-acting drugs (enalapril , fosinopril , perindopril , lisinopril , ramipril) are used to treat CHF .

The effectiveness of ramipril in relation to the prognosis of patients with CHF was demonstrated in the AIRE study (Acute Infarction Ramipril Efficacy), which included 2006 patients with signs of heart failure in the acute period of myocardial infarction. Ramipril (2.5–5 mg twice daily) or placebo was prescribed for at least 6 months (mean 15 months). Already in the first 30 days of observation, the mortality rate of patients receiving ramipril was 30% lower than in the placebo group (close to statistical significance; p = 0.053). Based on the results of the observation, it turned out that in the ramipril group , total and sudden cardiac mortality was statistically significantly lower (by 27% (p = 0.002) and by 30% (p = 0.011), respectively) than in the placebo group [3]. The 603 patients from this study were followed up in the AIREX study (AIRE Extension) for 3 years. Moreover, the relative risk of death from any cause was statistically significantly lower (by 36%) in patients taking ramipril [4]. In recent studies that compared the effectiveness of various ACEIs, the lowest incidence of overall mortality in patients with CHF was noted when using ramipril [5, 6].

The high safety and effectiveness of ramipril is emphasized by the fact that in the ongoing RASTAVI study (RAS blockade after TAVI) this drug was chosen to study the prognostic role of RAAS blockade in patients undergoing endovascular aortic valve replacement [7].

Typically, ramipril (Hartil) for CHF is prescribed starting with minimal doses (1.25–2.5 mg 1 time per day), increasing the dose by 1.25–2.5 mg every 1–2 weeks to the maximum tolerated (10 mg / day).

Angiotensin II receptor antagonists are prescribed in case of intolerance to ACE inhibitors (development of cough), subject to the same principles. It should be remembered that ACEI and ARAII cannot be used together. Like other vasodilators, they are not used in patients with valvular stenosis. Losartan , valsartan , and candesartan are used to treat CHF .

After the dose of the ACEI has been titrated, all clinically stable patients (in a state of compensation) without contraindications should be prescribed a beta blocker, also titrating the dose from the minimum to the maximum tolerated. At the same time , the patient’s well-being, auscultatory signs of bronchial obstruction, blood pressure and heart rate, ECG signs of conduction disorders and bradycardia are also monitored . The target heart rate values, reflecting adequate blockade of the sympathetic system, in patients with sinus rhythm are considered to be 60 per 1 min at rest, in patients with AF - no more than 110 per 1 min. Often, it may be necessary to study heart rate at night using 24-hour ECG monitoring . In patients with CHF of ischemic etiology, it is

advisable to first titrate the dose of a beta blocker, and then an ACEI or an ARA II. Bisoprolol , carvedilol and metoprolol are used to treat CHF sustained release succinate . In the presence of ventricular arrhythmias, sotalol may be considered , and in patients over 75 years of age, nebivolol .

Mineralocorticoid receptor antagonists (spironolactone and eplerenone) can be used in high doses to potentiate the diuretic effect of loop diuretics and in low doses for additional blockade of the RAAS in patients with a titrated dose of an AFPI or ARAII. Caution must be exercised when prescribing them to patients with a decrease in glomerular filtration rate and blood potassium levels >5 mmol /l. When prescribing AMKR Regular monitoring of potassium and creatinine levels , blood pressure, and the appearance of gynecomastia is required.

Relatively recently, a new class of drugs was developed that acts on the RAAS and the neutral endopeptidase system - ARNI (angiotensin receptor-neprilysin inhibitor – inhibitor of angiotensin II and neprilysin receptors). The first drug from this group is LCZ696, a substance that consists of fragments of valsartan and sacubitril (neprilysin inhibitor). This drug suppresses the secretion of renin and aldosterone, increases the excretion of sodium and water, and inhibits remodeling processes . Despite the superiority of this drug over ACE inhibitors, proven in clinical studies, its practical use is limited by its high cost.

Diuretics are prescribed to patients with CHF and fluid retention to reduce symptoms of congestion. Some patients with initial manifestations of CHF, without symptoms of fluid retention, do not need diuretics. The dose of diuretics is selected individually and, unlike ACE inhibitors and beta blockers, is titrated until the minimum effective is achieved. When prescribing diuretics, it is necessary to monitor the patient’s well-being, blood pressure, electrolyte and creatinine levels , and the volume of fluid consumed and excreted. In practice, accurate monitoring of urine output is difficult because it is difficult to take into account the fluid contained in food and excreted through sweat and breathing. Therefore, it is very important to monitor the patient’s body weight after waking up and going to the morning toilet on the same scales, in the same clothes. Typically, in decompensated patients, loop diuretics are used intravenously, in doses that allow an increase in the volume of excreted fluid by 800–1000 ml compared to consumed (and, accordingly, leading to a loss of body weight by 0.8–1 kg/ day). After getting rid of retained fluid and achieving “dry weight,” they move on to oral daily diuretics in lower doses, allowing them to maintain a stable body weight. An increase in body weight is a signal that it is necessary to consider increasing the dose of the diuretic. In some patients with developing resistance to diuretics, it is advisable to use drugs from several groups (loop, thiazide diuretics, AMKR, carbonic anhydrase inhibitor) with different points of application.

Digoxin in patients with CHF and AF

with a high frequency of ventricular response, since the drug has not only a positive inotropic, but also a negative chronotropic effect. If sinus rhythm persists, the use of digoxin remains at the discretion of the attending physician (for example, in patients in whom titration of ACE inhibitors and beta blockers is limited by hypotension). It is advisable not only to monitor the patient's well-being and heart rate, but also to laboratory determine the concentration of digoxin to avoid overdose.

Anticoagulants are used only in patients with CHF and AF or venous thromboembolism according to the appropriate principles. Antiplatelet agents are also prescribed to patients with CHF only if there are specific indications (atherosclerosis, primarily coronary artery disease), according to the rules described in the relevant guidelines.

Slow calcium channel blockers can reduce LV contractile function, so their use is avoided in patients with CHF. Drugs in this group can be considered in patients with hypertension that persists despite taking a titrated dose of ACE inhibitor/ARB, beta blocker and diuretic, or as an antianginal agent in patients with CHF and persistent angina despite taking beta blockers.

Pharmacotherapy of CHF- pEF (diastolic)

evidence that would allow us to formulate a clear algorithm for the treatment of CHF- pEF with drugs that reliably improve the prognosis of patients. However, practice shows that the use of the same classes of drugs that are used to treat systolic CHF often leads to a decrease in the severity of symptoms of diastolic CHF. In addition, the impact on the diseases that caused it is carried out using the same means. It is believed that drugs that lower heart rate (beta blockers, digoxin), prolonging diastole, improve LV filling, which suffers in CHF- pEF . Inhibitors of angiotensin-converting enzyme, APAII, AMKR reduce the severity of LV hypertrophy and fibrosis, improve relaxation and distensibility of the myocardium, which improves its diastolic properties. Diuretics in patients with LV diastolic dysfunction and congestion should be used with caution, since a decrease in circulating blood volume can lead to a decrease in LV diastolic filling and, accordingly, cardiac output.

Surgical and electrophysiological methods of treating CHF

One of the main mechanisms of death in patients with CHF, including sudden, is fatal rhythm disturbances, primarily ventricular arrhythmias and asystole. An implantable cardioverter -defibrillator continuously monitors the heart rhythm and, if ventricular tachycardia or ventricular fibrillation occurs, restores sinus rhythm with a low-force discharge. Implantation of a cardioverter -defibrillator should be considered in all patients with symptomatic CHF or LV dysfunction who have experienced cardiac arrest and/or symptomatic ventricular arrhythmias for secondary prevention of sudden

death. In patients who have had a myocardial infarction more than 40 days ago and have an EF≤35% and class II–III CHF, implantation of a cardioverter -defibrillator is considered as a method of primary prevention.

A special version of the three-chamber electrocardiostimulation , which restores correct interventricular interaction, which is often distorted in CHF and impaired intraventricular conduction, is cardiac resynchronization therapy. Cardiac resynchronization therapy as a method complementary to pharmacotherapy can be considered in patients with CHF with EF <35% and left bundle branch block starting from class II and with a QRS complex duration >120 ms , however, the greatest effectiveness of the procedure was noted in more severe patients - with III–IV FC and QRS complex duration ≥150 ms . Cardiac resynchronization therapy can increase EF, reduce symptoms of CHF and, most importantly, reduce mortality, including in patients with AF. Often the implanted device combines the functions of cardiac resynchronization therapy and a cardioverter -defibrillator.

Heart transplantation is the last chance to save the lives of patients with severe CHF, resistant to therapy, the impossibility of alternative treatment methods, irreversible structural changes in target organs, but with the potential to achieve remission after transplantation of a donor heart. The availability of heart transplantation is limited by the shortage of donor material. The issues of selecting recipients and drawing up a waiting list remain problematic from a medical and legal point of view. A limiting factor is the high cost of organizational support for both the operation and postoperative patient management, including immunosuppressive therapy to prevent transplant rejection.

With the progression of CHF and the development of resistance to therapy, in some cases the issue of using an artificial LV may be considered (left ventricular assist device , LVAD). The device, placed in the abdominal cavity, is powered from an external source. An outflow line is sewn into the apex of the LV, connected to a pumping device that sends blood to the aorta. Thus, the load on the LV is significantly reduced due to the operation of the pump. There are several options for such devices, including one installed endovascularly in the LV cavity microturbine , facilitating the pumping of blood from the LV to the aorta.

Indications for LVAD implantation are CHF, which remains, despite treatment, at the level of class IV, LVEF < 30%, dependence on intravenous inotropic support, and a progressive decrease in glomerular filtration rate. The use of such devices is currently considered not only as a bridge to heart transplantation in patients with terminal heart failure, but also as a way to improve prognosis and improve systolic function in such patients.

Non-drug treatment of CHF

Lifestyle modification is no less important in the treatment of CHF than pharmacotherapy. Despite the lack of time, it is the attending physician who must provide the patient with information about the need and methods of quitting smoking and drinking alcohol, and normalizing body weight. Overcoming the negativism that often arises in patients during a conversation about the need for dietary restrictions, one should clearly outline the need to bring the caloric content of food in line with energy costs (which are usually low in a patient with CHF), primarily by reducing the consumption of easily digestible carbohydrates and animal fats. It is also necessary to explain to the patient the importance of limiting the consumption of table salt. It is necessary to perform regular dosed physical activity (walking, gymnastics) that causes mild shortness of breath or palpitations. Excessive physical activity should be limited.

Managing a patient with CHF is not an easy task, but it can be done if you have a good knowledge of clinical recommendations. Improving the prognosis and quality of life of such patients is possible through the interaction of inpatient doctors, who often deal with decompensation of CHF, and outpatient doctors, who bear the burden of long-term care for patients and prevention of decompensation.

Bibliography

1. Karpov Yu.A., Kobalava Zh.D., Kuznetsov V.A., Lazebnik L.B., Nasonov E.L., Nedogoda S.V., Nikitin Yu.P., Oganov R.G., Panchenko E.P., Perepech N.B., Podzolokov V.I., Pozdnyakov Yu.A., Rakov A.L., Ruda M.Ya., Rylova A.K., Simonenko V.B., Sido - Renko B.A., Staroverov I.I., Sulimov V.B., Tarlovskaya E.I., Tereshchenko S.N., Fomina I.G., Chazova I.E. National recommendations of OSHF, RKO and RNMOT for the diagnosis and treatment of CHF (fourth revision). Approved at the OSSN congress on March 31, 2013 and the RKO congress on September 25, 2013.
2. Ponikowski P., Voors AA, Anker SD, Bueno H., Cleland JGF, Coats AJS, Falk V., González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M., Linde C., Nihoyannopoulos P., Paris - sis JT, Pieske B., Riley JP, Rosano GMC, Ruilope LM, Rus - chitzka F., Rutten FH, van der Meer P.; ESC Scientific Document Group . 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution - tion of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37(27): 2129–2200.
3. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Lancet 1993 ; 342(8875): 821–828.

4. Hall AS, Murray GD, Ball SG. Follow-up study of patients randomly allocated ramipril or placebo for heart failure after acute myocardial infarction: AIRE Extension (AIREX) Study. Acute Infarction - tion Ramipril Efficacy. Lancet 1997; 349(9064): 1493–1497.
5. Sun W., Zhang H., Guo J., Zhang X., Zhang L., Li C., Zhang L. Comparison of the efficacy and safety of different ACE inhibitors in patients with chronic heart failure: a PRISMA-Compliant network meta-analysis. Medicine (Baltimore) 2016; 95(6): e2554.
6. Pilote L., Abrahamowicz M., Eisenberg M., Humphries K., Behlou -li H., Tu JV Effect of different angiotensin-converting-enzyme inhibitors on mortality among elderly patients with congestive heart failure. CMAJ 2008; 178(10): 1303–1311.
7. Amat -Santos IJ, Catalá P., Diez Del Hoyo F., Fernandez-Diaz JA, Alonso-Briales JH, Del Trigo M., Regueiro A., Juan- Salvadores P., Serra V., Gutierrez- Ibanes E. ., Muñoz- García AJ, Nombela -Franco L., Sabate M., Jimenez-Diaz V.A., García Del Blanco B., López J., Varela-Falcón L.H., Sevilla T., Arnold R., Revilla A. , San Roman JA Impact of renin- angiotensin system inhibitors on clinical outcomes and ventricular remodeling after transcatheter aortic valve implantation : rationale and design of the RASTAVI randomized multicentre study. BMJ Open . 2018; 8(2): e020255.