ADVANCED HEART FAILURE

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Rezumat

Insuficiența cardiacă avansată (AHF) este stadiul insuficienței cardiace (IC) refractară la tratamentul medical maximal, dispozitive cardiace (CRT - resincronizare cardiacă, ICD - defibrilator implantabil) și tratament chirurgical. AHF a devenit actuală prin experiența și rezultatele favorabile ale tratamentului prin suport circulator mecanic (MCS) și transplant cardiac (CT).

Articolul trece în revistă criteriile de definire ale AHF (2018 ESC statement), istoria naturală și prognosticul în afara formelor de tratament avansat. Evaluarea factorilor de risc și de prognostic este necesară înainte de decizia tratament avansat: factorii clinici (severitatea IC și reducerea capacității funcționale cardiorespiratorii), funcția VD, markerii biologici și elementele de disfuncție de organ, precum și reducerea toleranței la medicația convențională.

În încheiere, sunt prezentate principiile de tratament și rezultatele prin suport circulator mecanic și transplant cardiac.

Cuvinte cheie: *insuficiența cardiacă avansată, suport circulator mecanic, transplant cardiac.*

Abstract

Advanced heart failure (AHF) is the stage of heart failure (HF) refractory to maximal medical treatment, cardiac devices (CRT - cardiac resynchronization, ICD - implantable defibrillator) and surgical treatment. AHF has become of interest through the experience and favorable results of treatment by mechanical circulatory support (MCS) and cardiac transplant (CT).

The article reviews the criteria for defining the AHF (2018 ESC statement), natural history and prognosis outside the advanced treatment forms. Evaluation of risk and prognostic factors is required before the decision of advanced therapy: clinical factors (HF severity and reduction of cardiorespiratory functional capacity), RV function, biological markers and elements of organ dysfunction, as well as reduction of tolerance to conventional medication.

Finally, the principles of treatment and the results of mechanical circulatory support and cardiac transplant are presented.

Keywords: *advanced heart failure, mechanical circulatory support, heart transplant.*

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The term “advanced heart failure” (AHF), generically used since 2007, defined the stage of heart failure (HF) in which maximal medical treatment, the use of cardiac devices and surgical procedures, were deemed insufficient for controlling its evolution⁽¹⁾. The term AHF is equal to the terms of “end stage heart failure”, class D or class IV NYHA HF.

Defining the criteria for AHF is necessary among cardiologists, given the recent treatment advances for the so-called “refractory” HF: mechanical circulatory support (MCS) devices and cardiac transplant. The first criteria for defining AHF were published by the Heart Failure Association of the ESC (2007) and it included signs and symptoms of progressive HF, objective evidence of severe cardiac dysfunction and the severe altered functional capacity. The American College of Cardiology / American Heart Association (2013)⁽²⁾ and the Heart Failure Society of America (2016)⁽³⁾, published mildly different criteria and indices compared to the 2007 HFA criteria. In 2018, the Heart Failure Association of the ESC published an extensive statement on AHF⁽⁴⁾.

Given the new data regarding AHF, discussed in the statements above, this paper will present the prevalence, the accepted criteria for defining AHF, the main negative predictors which guide patients towards advanced therapy and the general

guidelines for the management of AHF. It must be stressed that terms like acute and chronic HF, class I-IV NYHA HF, acutely decompensated chronic HF, HF with preserved or increased ejection fraction, worsening HF and refractory HF maintain their current accepted definitions. Patients from these types and classes of HF are selected for potential advanced therapies (mechanical circulatory support, cardiac transplantation) or end-of-life care programmes.

The prevalence of AHF is estimated based on its accepted definition. Data from the ADHERE Registry (Acute Decompensated Heart Failure National Registry) showed that about 5% of end-stage patients have signs and symptoms refractory to medical therapy and can be classified as AHF⁽³⁾. Other data estimate the prevalence of AHF as between 6% and 25%, depending on the used definition and the studied population⁽⁵⁾. In general, the prevalence estimation varies between registries, trials and the physiopathologic type of HF (with reduced or preserved HF). Patients with stage D HF are considered having AHF, as well as some patients in class NYHA III and IV that are refractory to optimal medical therapy.

The criteria for defining AHF according to the 2018 ESC statement are⁽⁴⁾:

1. Severe and persistent symptoms of class III and IV NYHA HF

2. Severe cardiac dysfunction defined by:
 - $FEVS \leq 30\%$
 - Isolated right heart failure
 - Severe inoperable valve disease
 - Inoperable congenital heart defects
 - Persistently increased NTproBNP levels and LV dysfunction (HFrEF and HFmEF)
3. Episodes of pulmonary or systemic congestion, requiring high doses of i.v. diuretics, combinations of diuretics, are resistant to diuretics or if low cardiac output is present, requiring inotropes or vasodilators or malignant arrhythmias are present.
4. The progressive reduction of exercise capacity (6 minutes walking test <300m) or $pVO_2 < 12-14$ ml/kg/min - of cardiac origin.

Additionally, persistent renal or hepatic dysfunction can be present, as well as type 2 pulmonary hypertension.

Heart disease patients which meet the criteria for AHF have a severely altered quality of life and limited life expectancy. These patients require clinical, biological evaluation, imaging and risk assessment (MAGGIC or SHFM) for inclusion in an advanced therapy programme: mechanical assist devices and cardiac transplantation⁽⁶⁾.

Natural history and prognosis

HF evolution is progressive and characterized by worsening signs and symptoms, having progressively shorter intervals of proper response to treatment. There are several factors which determine the progressive cardiac dysfunction which are mainly related to the progressive ventricular remodelling and its consequences: sympathetic nervous and renin-angiotensin system activation,

myocardial injury, etc. The initiation and continuation of maximal medical therapy (diuretics, ACE-I/ARB, sacubitril/valsartan, betablockers, MRA antagonists) reduces mortality between 17% and 30%⁽⁷⁾. Maximal treatment, at most, delays the progression towards AHF. Most medically managed patients die because of LV dysfunction (>90%), despite the use of inotrope and vasodilator therapy.

Inotropes (dobutamine, milrinone, levosimendan) used in acute HF and tissue hypoperfusion, as well as in acutely decompensated chronic HF, improves symptoms and functional capacity (including peripheral perfusion) while increasing myocardial oxygen demand, the arrhythmia risk and mortality⁽⁸⁾. The pharmacological effects of inotropes / vasodilators on peripheral vascular resistance, pulmonary capillary pressure, mean blood pressure and heart rate are different, but all increase (at different rates) the cardiac output.

Limited or prolonged administration of inotropes in AHF (class III or IV NYHA) is recommended as a "bridge" to implanting a mechanical circulatory assist device or cardiac transplantation. Increased dosages or prolonged administration favour the occurrence of lethal arrhythmias and negatively affect the prognosis⁽⁹⁾. On the other hand, the short-term administration of inotropes can be used in AHF patients with reduced cardiac output and organ dysfunction (renal or hepatic), coupled with cardiac resynchronization therapy (CRT), if indicated, until the HF signs and symptoms improve or advanced HF treatment measures are applied⁽⁴⁾.

The evolution of chronic HF with reduced ejection fraction under optimal medical therapy in patients who are ineligible for cardiac transplantation or MCS has been

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studied in the REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure). The survival in the medically managed group at 1 and 2 years was 25% and 8%, respectively, with a mean survival of 150 days⁽¹⁰⁾. Also, in the INTrEPID trial (Chronic Mechanical Circulatory Support for inotrope-Dependent Heart Failure Patients who are non Transplant Candidates), survival in the inotrope managed group was 22% at 6 months and 11% at 1 year⁽¹¹⁾.

HF evolution towards AHF can be delayed by CRT or ICD implantation. The 2013 ESC guidelines recommend CRT device implantation in HF patients with a LVEF of <35% and LBBB duration >130 msec which remain in class NYHA III or ambulatory NYHA IV, despite optimal medical therapy⁽¹²⁾. Newly published data suggest that CRT can be used in sinus rhythm, as well as atrial fibrillation patients, in patients with a previous pacemaker or ICD implantation.

The benefit of CRT, using the above criteria, has been shown in numerous randomized trials, including the REVERSE trial (Resynchronization Reverse Remodelling in Systolic Left Ventricular Dysfunction)^(14,15).

Cardiac resynchronization therapy improves HF symptoms, reduces hospitalization rate, induces reverse remodelling, improves the mitral regurgitation grade and reduces mortality in selected patients with increased

duration of LBBB, left ventricle dysfunction (class III or IV NYHA) already on optimal medical therapy^(13,16).

ICD implantation in HF patients with an increased risk of fatal arrhythmias can avoid sudden cardiac death. In general, sudden cardiac death accounts to a third to a half of all mortality through HF. Malignant arrhythmia triggers (VT, VF) in HF or cardiomyopathies can usually be identified, treated or prevented: myocardial ischemia, electrolyte imbalance (increased or decreased K levels, hypomagnesemia), the proarrhythmic effects of certain drugs, excessive sympathetic nervous system activation.

Risk factors and prognosis

When AHF is suspected, the identification of the main risk factors associated with a poor HF prognosis and evaluation for advanced HF therapies are necessary (mechanical circulatory support or cardiac transplantation).

There are several risk factors associated with a poor prognosis in AHF. Some are general (age, comorbidities, renal dysfunction, biological status, etc.), others being specific (clinical factors, right and left heart function, biological data, tolerance or intolerance to cardiac therapy)⁽¹⁸⁾. The clinical factors are mainly related to HF severity and the

reduction of cardio-respiratory functional capacity, analysed by objective means.

Fully medicated class IV HF patients have an annual mortality of 64%, compared to approximately 15% of those in NYHA III class^(19,20). Time since first diagnosis of HF and repeated hospital admissions (over 1-2 annually) are important risk factors. The mortality risk increases after each new hospital admission, adjusted for age and renal function.

Non-invasive assessment of the functional capacity is possible by cardio-respiratory exercise testing. In advanced HF patients, a maximum O₂ consumption <10-12 ml/kg/min (pO₂) is a potential indicator for MCS or cardiac transplantation^(4,21). The 6 minutes walking test is used as screening for AHF (<300 m) and is performed, in the hospital, in patients who cannot perform the cardio-pulmonary exercise test. Moreover, the 6MWT identifies frail HF patients with a global dysfunction, weight loss and reduced physical activity. A direct link between frailty and HF mortality has been established⁽²²⁾. This type of patients is not eligible for mechanical circulatory support.

The clinical exam of AHF patients can identify additional risk factors: sarcopenia and cachexia (catabolic status, increased inflammatory cytokines), resting heart rate (sinus rhythm, tachyarrhythmias), low mean blood pressure, ECG suggesting myocardial ischemia or intraventricular conduction disturbances⁽¹⁸⁾.

Right ventricular (RV) function is a major prognostic factor in AHF patients. RV dysfunction can be isolated (resulting from an intrinsic cardiomyopathic process), but also secondary to type 2 pulmonary hypertension (due to LV dysfunction). RV performance is a predictor of morbidity and mortality in HF, pulmonary hypertension,

coronary artery disease, cardiomyopathy and ventricular assist devices patients. The standard echocardiogram is a dependable tool for assessing RV function, but the 3D evaluation allows RV ejection fraction measurements, with an accuracy comparable to cardiac MRI ("the gold standard"). An EF <35% and TAPSE <17 mm are considered markers of RV dysfunction. An RVEF of above 35% is more strongly associated with improved survival, being of even better prediction compared to the maximum O₂ uptake⁽²³⁾.

RV failure and congestive hepatomegaly contribute to metabolic imbalances (the synthesis function, sarcopenia and cachexia) and to the progression of systemic congestion.

The early recognition and treatment of RV failure and pulmonary hypertension is essential, as they are major risk factors, and influence the eligibility for MCS or cardiac transplantation⁽⁴⁾.

Biological factors that are associated with a poor prognosis are common in worsening chronic HF, as well as in AHF. The difference between these risk factors relates to their levels and their progressive nature (despite optimal medical therapy) in AHF.

The main biological risk factors associated with a poor prognosis in AHF are:

- High NTproBNP levels – and its increase as a marker of cardiac myocyte stress. There is a progressive increase of the relative risk of death in relation to the BNP level⁽²⁴⁾. Other cardiac biomarkers such as s/ST2 and galactine-3 – markers of cardiac stress / oxidative stress / fibrosis – which are frequently abnormal in HF and carry a role in the prognosis evaluation.
- Increased hs-TnT levels – above the reference limit, its persistence or

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increase, is a marker of myocardial injury (acute or chronic).

- Drug induced electrolyte imbalance – but also spontaneous, if uncorrected, is associated with a poor HF prognosis; hyponatremia (<135 mmol/l), hypokalemia and hypernatremia. In an older trial, a sodium level of below 137 mmol/l was the strongest predictor of long term HF mortality⁽²⁵⁾. The prognostic role of hyponatremia was demonstrated in recent studies⁽²⁶⁾.
- AHF can be accompanied by organ dysfunction, especially in conditions of low cardiac output, severe systemic congestion and inadequate medication.
- Renal dysfunction (the cardiorenal syndrome) is common in AHF, due to a combination of: reduced renal perfusion, neurohormonal hyperstimulation, increased venous pressure and RV dysfunction⁽²⁷⁾. The renal function can be affected by increased diuretic doses and by the development of resistance to diuretics. The cardiorenal syndrome can negatively impact the outcome after mechanical assist device implantation in AHF patients⁽²⁸⁾. Also, AHF patients can develop congestive liver disease and low cardiac output, ischemic (hypoxic) hepatitis – defined

as the increase of liver enzymes by 10-20% above the upper limit of normal and LDH increase – with rapid regression (by hemodynamic improvement) or acute liver failure.

- Drug intolerance – is an important factor in the evolution on chronic HF patients. Not all patients with NYHA III or IV class HF or refractory HF tolerate the prescribed drug dosages recommended as optimal therapy in the guidelines: diuretics, ACE inhibitors, sacubitril/valsartan (for HFrEF), betablocker, MRA antagonists. About 1/3 of AHF patients do not tolerate ACE inhibitors, even in small doses, because of the worsening of the renal dysfunction or hypotension. Patients who do not tolerate ACE inhibitors have an increase of 2.5x incidence of death⁽²⁹⁾. Betablocker tolerance can also be limited by hypotension, bradycardia and worsening fatigue.

The multiple risk factors associated with the progression of HF to AHF lead to the integration of several prognostic markers into scores, which may identify which patients could most probably benefit from mechanical assist devices or transplantation.

The most well-known are the SHFs (Seattle Heart Score)⁽³⁰⁾ and MAGGIC (Metanalysis Group in Chronic Heart Failure) scores which

have a similar predictive accuracy for the AHF prognosis⁽³¹⁾.

Treatment principles in AHF

The progressive nature of end stage heart failure (refractory HF) severely impacts the quality of life, morbidity and mortality. The 5-year mortality of symptomatic HF patients is about 50%, but reaches 80% per year in refractory (stage D) HF patients, after optimal medical therapy and resynchronization therapy, where indicated⁽⁶³⁾.

Currently, the treatment options for managing AHF include: mechanical circulatory support (MCS), cardiac transplantation, inotropes and palliative care. Different types of MCS and/or transplant are associated with a survival between 23% and 90% at 1 year⁽³²⁾.

The use of mechanical circulatory assist devices (MCS) for the short- or long-term management of AHF lately increased in the USA, to over 2500 units per year⁽³³⁾. In spite of this increase, the number of patients in which implants are performed is limited compared to the increasing prevalence of AHF. The proportion of patients with AHF which are candidates for MCS in the US was 27.4% in 2013 and it increases annually⁽³⁴⁾.

Evidence of their efficiency were first observed in the REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure), confirmed in subsequent trials which revealed a survival rate above 50% in the first to 5 years after implantation⁽³³⁾.

The mechanical circulatory support improves the survival and the quality of life of inotrope-dependent AHF patients and in those with contraindications for cardiac transplantation⁽³³⁾. MCS can be classified according to the time needed for circulatory support (short

or long-term), the implant's location (most of them being internal) and the type of flow (continuous or pulsatile, with an axial or centrifugal pump, respectively).

Several generations of MCS devices were tested (I, II, III), the most used being devices of the second generation, with continuous flow obtained by a centrifugal pump. The device's configuration varies, depending on the decision of the medical team which recommends the implantation of such a device taking into consideration the particular conditions of each patient.

Most devices are left ventricular assist devices (LVAD).

The time interval for using MCS devices is either short-term (days/weeks) or long-term, much more frequently, as a bridge to myocardial recovery or cardiac transplantation, and sometimes as destination therapy.

Short-term usage of assist devices (5-6 days) is most frequent in cardiogenic shock. The Impella device (Impella ventricular support system) is an axial flow pump which is placed through the aortic valve and aspirates blood from the LV and pumps it into the ascending aorta. The potential benefit includes: circulatory support (vital organ perfusion), the reduction of ventricular load and intracardiac filling pressure (reduces systemic congestion) and improves myocardial perfusion⁽³⁶⁾. The same circulatory and systemic effects can also be obtained through the Tandem Heart device, which connect the left atrium to the ilio-femoral artery. For insuring an adequate respiratory support, a membrane oxygenator can additionally be used⁽⁴⁾.

Both devices have numerous contraindications and complications, and are used for a short term in limited clinical scenarios.

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Long-term MCS devices (LVADs) are used in AHF patients as “destination therapy” or “bridge to transplant”⁽³⁶⁾. The most used pump-based devices are HeartMate II, HeartMate III, HeartWare Ventricular Assist Device (HVAD) and CentriMeg (St. Jude). The REMATCH trial (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) was the first to demonstrate the improvement of 1-year survival in patient ineligible for transplantation who were treated with LVADs, but 2-year survival was not statistically significant different⁽¹⁰⁾.

The selection of patients eligible for long-term MCS is made by a medical team and is similar to that of cardiac transplantation, according to the criteria of the International Society for Heart and Lung Transplant⁽³⁷⁾. The INTERMACS 1-7 profiles (International Registry for Mechanically Assisted Circulatory Support) are usually used for patient selection.

The INTERMACS 1 profile indicates cardiogenic shock (limited time decision), while the INTERMACS 2 profile equates to the failure of optimal medical therapy and the need for inotropes in AHF patients. Profiles 3-7 include class III or IV AHF patients which are non-inotrope dependent and are not candidates for cardiac transplantation^(38,39).

The contraindications for long-term MCS are:

- Extracardiac – severe renal or liver failure, advanced lung disease,

systemic infection, neurocognitive disease

- Cardiovascular – severe LV or RV dysfunction, high pulmonary vascular resistance, advanced peripheral artery or aortic disease^(4,40).

The benefits of LVAD are hemodynamic (LV unloading, LA volume reduction, increased PAM and increased coronary artery perfusion), as well as survival, NYHA class (up to class I and II NYHA in 80-85% of patients) and quality of life improvement⁽³³⁾.

The limiting factors of MCS after implantation are the prolonged and difficult rehabilitation and the complications: pump thrombosis and malfunction, infection, stroke (ischemic, embolic or ischemic encephalopathy), bleeding (especially gastrointestinal) and aortic regurgitation^(12,40).

Cardiac transplantation currently is the optimal and preferred treatment of selected AHF patients. 1-year survival after transplantation in about 90%, significantly higher the expected one in AHF patients. The improvement of the prognosis requires an optimal selection of the donor and recipient, adequate immunosuppression and treatment of opportunistic infections⁽⁴⁰⁾.

Unfortunately, the number of donors is significantly lower than that of potential recipients. Moreover, transplantation candidates are nowadays older (improved survival by advances in HF drugs), have

limiting comorbidities (diabetes, kidney disease) and risk of graft rejection.

AHF patients eligible for a heart transplant need a complex evaluation⁽⁴⁾. This requires a full clinical examination, echocardiogram and other imaging modalities, right heart catheterization, pulmonary artery pressure measurement, nutritional status assessment, and renal, liver and pulmonary function measurements. At the same time, the identification of contraindications is necessary, which include: active infection, systemic infection with multiple organ dysfunction, cancer, advanced atherosclerosis and its complications (ex. Stroke), other comorbidities which can significantly impact prognosis, and screening for HCV and HIV. Finally, the psychosocial status of the patient must be taken into account as well as other factors which can favor an improved outcome after transplantation (tolerance to immunosuppressive treatment, adherence and regular medical checks, family and environmental support).

Establishing which patients are fit for transplant is the responsibility of a medical team which consists of: a cardiologist specialized in AHF, cardiac surgeon, an anesthesia and intensive cardiac care specialist, and specialists in various fields such as: immunology, hemodynamics, imaging and laboratory medicine. The medical team assesses the risk in the absence of a heart transplant, analyzes if all therapeutic options are exhausted, establishes the timing of the transplant and decides in what center the transplant should take place. Usually, cardiac transplantation is reserved for NYHA IV patients, who had no improvement after optimal medical therapy, inotropes and mechanical circulatory support and cardiac or extracardiac contraindications are absent.

It is recommended that the cardiac transplant be performed (excluding emergencies) while the patient is in a as stable as possible condition, using prolonged inotrope administration and MCS devices. In about 50% of cases, MCS as a “bridge to transplant” is necessary to obtain a stable hemodynamic state before transplantation.

Conclusion

In conclusion, heart transplantation improves survival, exercise capacity and the quality of life, allows social reintegration, but is dependent on the adequate patient selection – usually according to the transplant centers guidelines^(9,41).

Palliative care comprises of a set of psychosocial and logistic measures that are necessary for patients who are unfit for advanced cardiac therapies (heart transplantation, MCS) and in which HF progresses⁽⁴³⁾. The decision for palliative care is also necessary in patients towards end-of-life in which advanced therapies have failed.

The measures through which an improvement of the quality of life as well as a reduction in anxiety and depression can be obtained are established by a multidisciplinary team for in-hospital or homebound patients. Each patient requires an individual medical and non-medical care plan which can make the progressive decline of all aspects of daily life tolerable^(4,43).

References

1. Metra M, Ponikowski P, Beckenstein K et al. Advanced chronic heart failure: a position statement from the study Group on Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology, *Eur J Heart Fail.* 2007, 9: 684-94
2. Allen LA, Stevenson LW, Grady KL et al - Decision making in advanced heart failure: a scientific statement from the American Heart Association, *Circulation* 2012, 125 (15):1928-52
3. Fang JC - Advanced (stage D) heart failure: a

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statement from the Heart Failure Society of America guidelines committee, *J Card Fail* 2015, 21 (6):519-34

4. Crespo-Leriro MG et al – Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology, *Eur J Heart Fail.* 2018, 20: 1505-1535

5. Abonezzedine OF, Redfield MM – Who has advanced Heart Failure? Definition and epidemiology, *Congest. Heart Fail* 2011, 17 (4): 160-8

6. Metra M, Dinatolo E, Dasseni A – The New Heart Failure Association. Definition of Advanced Heart Failure, *Cardiac Failure Rev* 2019, 5(1): 5-8

7. Fonarow GC, Yancy CW, Hernandez AF et al – Potential impact of optional implementation of evidence-based heart failure therapy on mortality, *Am Heart J* 2011, 161(6):1024-30

8. Ginwalla M, Tofovic – Current status of inotropes in heart failure, *Heart Failure Clin* 2018, 14: 601-616

9. Hashim T, Sanam K, Ravilla-Martinez et al – Clinical characteristics and outcomes of intravenous inotropic therapy in advanced heart failure, *Circ Heart Failure* 2015, 8:880-886

10. Rose EA, Gelijns AC, Moskowitz AJ et al – Long term use of left ventricular assist device for end-stage heart failure. The Randomized Evaluation of the Mechanical Assistance the Treatment of Congestive Heart Failure (REMATCH) Study Group, *N Engl J Med* 2001, 345(20):1435-43

11. Rogers JG, Butler J, Lansman SL et al – Chronic mechanical circulatory support for inotrope-dependent heart failure patients who are not transplant candidates: results of the INTrEPID Trial, *J Am Coll Cardiol* 2007, 50 (8) 241-7

12. Brignole M, Auricchio A, Baron-Esquivias G et al – Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on Cardiac Pacing and Desynchronization Therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA), *Eur Heart J* 2013, 34: 2281-392

13. Bariani G, Nesti M, Ziacchi M et al – Cardiac resynchronization on therapy: an Overview on

Guidelines, Heart Fail Clin 2017, 13:117-237

14. Abraham WT, Fisher WG, Smith AL et al – Cardiac resynchronization in chronic heart failure, *N Engl J Med* 2002, 346(24):1845-53

15. Linde C, Abraham WT, Gold MR et al – Randomized trial of resynchronization in mildly symptomatic Heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms, *J Am Coll Card* 2008, 52:1834-43

16. McAlister FA, Ezekowitz J – Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction, *JAMA* 2007, 297: 2502-2514

17. Frohlich GH, Holzmeister J, Hubler M et al – Prophylactic implantable cardioverter defibrillator treatment in patients with end-stage heart failure awaiting heart transplantation, *Heart* 2013, 99:1158-1165

18. Chaudhry Sunit-Preet, Stewart GC – Advanced Heart Failure: Prevalence, Natural History and Prognostic, *Heart Failure Clin* 2016, 12:323-333

19. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients, with reduced left ventricular ejection fraction. The SOLVD Investigators, *N Engl Med* 1992, 327(10): 682-91

20. Greenberg B, Lottes SR, Nelson JJ et al – Predictors of clinical outcomes in patients given carvedilol for heart failure, *Am J Cardiol* 2006, 98 (1): 1480-4

21. Corra U, Agostoni PG, Anker SD et al – Role of cardiopulmonary exercise test in clinical stratification in heart failure, *Eur J Heart Fail.* 2018, 20, 3-15

22. Cacciatore F, Abete P, Mazzarella F et al – Frailty predicts long-term mortality in elderly subjects with chronic heart failure, *Eur J Clin Invest* 2005, 35 (12):723-30

23. Di Salvo TG, Mathier M, Semigran MJ et al – Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure, *J Am Coll Cardiol* 1995, 25 (5): 1143-58

24. Doust JA, Pietrzak E, Dobson A et al. How well does B-type natriuretic peptide predicts death and cardiac events in patients with heart failure: systematic review, *BMJ* 2005, 330(7492): 625

25. Lee WH, Parker M – Prognostic importance of serum sodium concentration and its modification by converting-enzyme inhibition in patients with severe heart failure, *Circulation* 1986, 73(2): 257-67
26. Cutbert JJ, Pellicori P, Rigby et al – Low serum chloride in patients with chronic heart failure: clinical association and prognostic significance, *Eur J Heart Fail* 2018, 20:1426-35
27. Bock JS, Gottlich SS – Cardiorenal syndrome: new perspectives, *Circulation* 2010, 121 (23): 2592-600
28. Kirklin JK, Nafel BC, Kormos RL et al – Quantifying the effect of cardiorenal syndrome on mortality after left ventricular assist device implant, *J Heart Lung Transplant* 2013, 32(21): 1205-13
29. Kiftleson M, Hurwitz S, Shah MR et al – Development of circulatory renal limitation to angiotensin-converting enzyme inhibitors identifies patients with severe heart failure and early mortality, *J Am Coll Cardiol* 2003, 41 (11): 2029-35
30. Levy WC, Mozaffarian D, Linker DT et al – The Seattle Heart Failure model: predictor of survival in heart failure, *Circulation* 2006, 113 (11): 1424-33
31. Rusinaru D, Tribouilloy C, Berry C et al – Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: an individual patient data meta-analysis: meta analysis global group in chronic heart failure (MAGGIC), *Eur J Heart Fail* 2013, 14(10): 1139-46.
32. Wagas M, Cowger JA – Role of durable mechanical circulatory support for the management of advanced heart failure, *Heart Fail Clin* 2013, 12:399-409
33. Kirklin JK, Nashel DC, Pagani FD – Seventh INTERMACS annual report: a 15000 patients and counting, *J Heart Lung Transplantation* 2015, 34:1495-534
34. Colvin-Adams M, Swith JM, Heubner BM et al – OPTSRTR 2013 annual data report: *Am J Transplant* 2015, 15 (suppl 2)
35. Ponikowski P, Voeckler AA, Anker SD – 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 of the Heart Failure Association (HFA) of the ESC, *Eur J Heart Failure* 2016, 18:891-975
36. Klein L, Dorobantu L – Mechanical Circulatory Support in Current Approach to Heart Failure - Eds Dorobantu L et al, Springer 2016; pag: 311-333
37. Felman D, Pamboukian SV, Teuteberg I et al – The 2013 International Society for Heart and Lung Transplantation. Guidelines for mechanical circulatory support executive summary, *J Heart Lung Transplant* 2013, 22:157-82
38. Boyle AJ, Ascheim DD, Russo MJ et al – Clinical outcomes for continuous flow left ventricular assist device patients stratified by pre-operative INTERMACS classification, *J Heart Lung Transplant* 2017, 30:402-407
39. Jurda UP, Kushwaha SS, Tatroles AJ et al – Results of the destination therapy post-food and drug administration approval study with a continuous flow left ventricular device : a prospective study using the INTERMACS Registry, *J Am Coll Cardiol* 2014, 63:1751-1757
40. Kittleston MM – Changing role of Heart Transplantation, *Heart Fail Clin* 2016, 12:411-421
41. Kalmanovici I et al – Management of Advanced Heart Failure, *Expert Rev. Cardiovasc. Therapy*, 2013, 16(11); 775-794
42. Melra MR, Canter CE, Hannan MM et al – The 2016 International Society of Heart Lung Transplantation listing criteria for heart transplantation: a 10 year update, *Heart Lung Transplant* 2016, 75: 1-23
43. Campbell RT, Petric MC, Jackson CE et al – Which patients with heart failure should receive specialist palliative care, *Eur J Heart Fail*. 2018, 20: 1338-47