Liječenje uznapredovalog zatajivanja srca

Treatment of advanced heart failure

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SAŽETAK: Uznapredovalo zatajivanje srca (ZS) karakterizirano je refraktornim simptomima i učestalim rehospitalizacijama unatoč primjeni optimalne medikamentne terapije (OMT). Prevalencija terminalnog ZS-a u porastu je zbog sve većega broja bolesnika s čimbenicima rizika za kardiovaskularne bolesti i starenja populacije te je velik klinički izazov i opterećenje za zdravstveni sustav. Prognoza je bolesti loša s jednogodišnjim mortalitetom od 25 do 75 %. S obzirom na to da je OMT ograničena učinka, u liječenju takvih bolesnika razmatraju se napredne terapijske metode koje uključuju transplantaciju srca i ugradnju mehaničke cirkulacijske potpore. Transplantacija srca zlatni je standard liječenja terminalnog ZS-a, no zbog ograničena broja donorskih organa i postojanja određenih kontraindikacija, dio bolesnika neće moći biti liječen ovom metodom. Kratkoročni uređaji za mehaničku cirkulacijsku potporu mogu se rabiti u liječenju kardiogenog šoka i akutnog pogoršanja kao premoštenje do odluke, oporavka, nadogradnje potpore ili transplantacije srca. Dugoročni uređaji za potporu lijevoj klijetki ugrađuju se kao premoštenje do transplantacije srca ili kao destinacijska terapija u bolesnika koji su trajno nepogodni za transplantaciju srca. Glavni izazov u adekvatnoj primjeni transplantacije srca jest nerazmjer između potrebe i pojavnosti donora, što zahtijeva najbolji probir kandidata i bolju racionalizaciju resursa. Unatoč napretku tehnologije uređaja za mehaničku cirkulacijsku potporu, njihov pun potencijal ograničen je još uvijek nedovoljno razvijenom dugoročnom potporom za desnu klijetku, nerazvijenim potpunim intrakorporalnim sustavom, cijenom, odnosno dostupnošću, te mogućim neželjenim događajima nakon ugradnje kao što su infekcije provodnika, tromboza sustava ili krvarenje. Primjena naprednih metoda liječenja ZS-a u pomno selektiranih bolesnika ključna je za uspješan ishod. Prekasno upućivanje ovakvih bolesnika u transplantacijske centre dodatno ograničava terapijske opcije. U ovome preglednom radu prikazani su izazovi u liječenju bolesnika s terminalnim ZS-om uz osvrt na samu bolest, farmakoterapiju i primjenu naprednih metoda liječenja.

SUMMARY: Advanced heart failure (HF) is characterized by refractory symptoms and frequent rehospitalizations despite the optimal medical therapy. The prevalence of end-stage HF is increasing due to the increasing number of patients with risk factors for cardiovascular diseases and the ageing of the population, and it is a great clinical challenge and burden for the healthcare system. The prognosis of the disease is poor, with a one-year mortality rate of 25% to 75%. Given that the optimal medical therapy is of limited effect, advanced therapeutic methods which include heart transplantation and the mechanical circulatory support are being considered in the treatment of such patients. Heart transplantation is the gold standard for the treatment of end-stage HF, but due to the limited number of donor organs and certain contraindications, some patients will not be treated with this method. Short-term devices for mechanical circulatory support can be used in the treatment of cardiogenic shock and acute deterioration as a bridge to decision, recovery, upgrade or heart transplantation. Long-term devices for left ventricular support are implanted as a bridge to heart transplantation or as destination therapy in patients who are permanently ineligible for heart transplantation. The main challenge in the adequate use of heart transplantation is the disproportion between the need and the number of donors, which requires optimal screening of candidates and better rationalisation of resources. Despite advances in the technology of the devices for mechanical circulatory support, their full potential is limited due to the still underdeveloped long-term right ventricular support, the underdeveloped complete intracorporeal system, the cost (availability) and possible adverse events after implantation such as driveline infections, systemic thrombosis or bleeding. Application of advanced methods of treating HF in carefully selected patients is essential for a successful outcome. Delayed referral of such patients to transplant centres further limits therapeutic options. This paper presents the challenges in the treatment of patients with end-stage HF with reference to the disease itself, pharmacotherapy and the use of advanced treatment methods.

KLJUČNE RIJEČI: uznapredovalo zatajivanje srca, farmakoterapija, napredne metode liječenja, transplantacija srca, mehanička cirkulacijska potpora

KEYWORDS: advanced heart failure, pharmacotherapy, advanced treatment methods, heart transplantation, mechanical circulatory support.

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Uvod

Zatajivanje srca (ZS) klinički je sindrom uzrokovan različitim strukturnim i/ili funkcionalnim abnormalnostima srca koje dovode do smanjena srčanog volumena i/ili povišenoga tlaka punjenja klijetki u mirovanju ili naporu. Karakteriziraju ga simptomi poput zaduhe i općeg zamora te znakovi poput povišenoga jugularnoga venskog tlaka, plućnih krepitacija i perifernih edema[1].

Procjenjuje se da 64,3 milijuna ljudi u svijetu boluje od ZS-a. Prevalencija iznosi oko 1 – 2 % u odrasloj populaciji i raste s dobi. U starijih od 70 godina ukupna je prevalencija više od 10 %. ZS znatno utječe na kvalitetu života bolesnika i karakteriziran je visokim mortalitetom i morbiditetom[1-5]. Jones *i sur.* proveli su metaanalizu koja je uključivala više od 1,5 milijuna bolesnika sa ZS-om te je jednogodišnje preživljenje procijenjeno na 86,5 %, dvogodišnje na 72,6 %, petogodišnje na 56,7 % i desetogodišnje na 34,9 %[6].

ZS je sve veći financijski problem zbog velike ukupne cijene liječenja, a procjenjuje se da se u razvijenim zemljama oko 2 – 3 % ukupnih troškova zdravstvenog sustava odnosi upravo na liječenje ZS-a. Također se predviđa da će se broj bolesnika sa ZS-om povećati za 46 % i da će se troškovi vezani uz ZS povećati za 127 % u razdoblju od 2012. do 2030. godine[7,8].

Kronični ZS u konačnici napreduje do terminalnoga stadija bolesti koji je karakteriziran lošom prognozom, odnosno jednogodišnjim mortalitetom u rasponu 25 – 75 %. Bolesnici s akutnim ZS-om također se mogu prezentirati u uznapredovaloj kliničkoj slici. Procjenjuje se da je 1 – 10 % bolesnika sa ZS-om u terminalnom stadiju, a prevalencija je u kontinuiranom porastu zbog starenja populacije i sve većega broja bolesnika sa čimbenicima rizika za razvoj kardiovaskularnih bolesti[1,9].

Uznapredovalo ili terminalno zatajivanje srca

Prema HFA-ESC-u, za definiranje terminalnog ZS-a moraju biti zadovoljeni svi sljedeći kriteriji unatoč optimalnoj terapiji temeljenoj na smjernicama (GDMT):

1. teški i perzistentni simptomi ZS (NYHA III. ili IV. stupanj),
2. teška disfunkcija srca karakterizirana minimalno jednim od sljedećih kriterija:
   - reducirana ejekcijska frakcija lijeve klijetke (LVEF) ≤ 30%
   - izolirano zatajivanje desne klijetke
   - neoperabilne teške valvularne greške
   - neoperabilne teške kongenitalne greške
   - perzistentno visoke (ili rastuće) vrijednosti moždanoga natriuretskog peptida (BNP) ili N-terminalnog pro-B tipa natriuretskog peptida (NT-proBNP) i podatak o teškoj dijastoličkoj disfunkciji ili strukturnim abnormalnostima lijeve klijetke,
3. epizode plućne ili sistemske kongestije koje zahtijevaju visoku dozu intravenskih diuretika (ili kombinacije diuretika); ili epizode smanjenoga minutnog volumena koje zahtijevaju inotropnu potporu ili primjenu vazoaktivnih lijekova; ili maligne aritmije koje uzrokuju >1 neplaniranih posjeta liječniku ili hospitalizacija u posljednjih 12 mjeseci,
4. značajna netolerancija napora s nemogućnošću provođenja tjelesne aktivnosti ili prehodana udaljenost na šestminut-

Introduction

Heart failure (HF) is a clinical syndrome caused by various structural and/or functional abnormalities of the heart that lead to reduced cardiac output and/or increased ventricular filling pressure at rest or exercise. It is characterized by symptoms such as shortness of breath and general fatigue, and signs such as increased jugular venous pressure, lung crepitations and peripheral edema[1].

It is estimated that 64.3 million people in the world suffer from HF. The prevalence is about 1–2% in the adult population and increases with age. In people over the age of 70, the total prevalence is above 10%. HF significantly affects the patients' quality of life and is characterized by high mortality and morbidity[1-5]. Jones et al. conducted a meta-analysis that included more than 1.5 million patients with HF and estimated one-year survival at 86.5%, two-year at 72.6%, five-year at 56.7% and ten-year at 34.9%[6].

HF represents an increasing financial problem due to the high total cost of treatment, and it is estimated that in developed countries about 2–3% of the total health system cost relate to the treatment of HF. Furthermore, it is predicted that the number of patients with HF will increase by 46% and that HF-related costs will increase by 127% in the period from 2012 to 2030[7,8].

Chronic HF ultimately progresses to the end stage of the disease, which is characterized by poor prognosis, i.e. one-year mortality ranging between 25% and 75%. Patients with acute HF can also present with an advanced clinical picture. It is estimated that 1–10% of patients with HF are in the end stage, and the prevalence is continuously increasing due to the ageing of the population and the increasing number of patients with risk factor for cardiovascular diseases[1,9].

Advanced or end-stage heart failure

According to the Heart Failure Association of the European Society of Cardiology (HFA-ESC) all the following criteria must be met to define end-stage HF despite the optimal guideline-directed medical therapy (GDMT):

1. severe and persistent symptoms of HF (NYHA class III or IV),
2. severe cardiac dysfunction characterized by at least one of the following criteria:
   - reduced left ventricular ejection fraction (LVEF) ≤ 30%
   - isolated right ventricular failure
   - inoperable severe valvular disease
   - inoperable severe congenital defects
   - persistently high (or increasing) levels of brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) and presence of severe diastolic dysfunction or structural abnormalities of the left ventricle,
3. episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or combinations of diuretics); or episodes of reduced cardiac output that require inotropic support or the use of vasoactive drugs; or malignant arrhythmias causing > 1 unplanned visit to the doctor or hospitalization in the last 12 months,
4. significant exercise intolerance with the inability to perform physical activity or the six-minute walk test (6MWT)

nom testu hodanja (6MWT) <300 m ili vršna potrošnja kisika (peakVO2) na testu opterećenjem <12 – 14 mL/kg/min, za koje se pretpostavlja da su srčane etiologije.

Važno je istaknuti da se definicija terminalnog zatajivanja odnosi na ZS s reduciranom, ali i očuvanom ejekcijskom frakcijom[9].

Predložena je i univerzalna definicija terminalnog ZS-a prema HFSA-u, HFA-ESC i JHFS. Prema konsenzusu, terminalni ZS definira se kao stadij D koji je obilježen teškim simptomima i/ili znakovima ZS-a u mirovanju, učestalim rehospitalizacijama unatoč GDMT-u, bolesnici su refraktorni ili ne toleriraju GDMT, što zahtijeva razmatranje transplantacije srca, ugradnju uređaja za mehaničku cirkulacijsku potporu (MCS) ili palijativnu skrb (PC) (**slika 1**)[10].

< 300 m or the peak oxygen consumption (peakVO2) on the exercise test < 12–14 mL/kg/min, which are assumed to be of cardiac aetiology.

It is important to point out that the definition of end-stage HF refers to heart failure with reduced but also with preserved ejection fraction[9].

A universal definition of end-stage HF was also proposed by the Heart Failure Society of America (HFSA), HFA-ESC and the Japanese Heart Failure Society (JHFS). According to the consensus, end-stage HF is defined as stage D, which is characterized by severe symptoms and/or signs of HF at rest, frequent rehospitalizations despite GDMT, patients are refractory or do not tolerate GDMT, which is why it is necessary to consider heart transplantation, implantation of a mechanical circulatory support (MCS) or palliative care (PC) (**Figure 1**)[10].

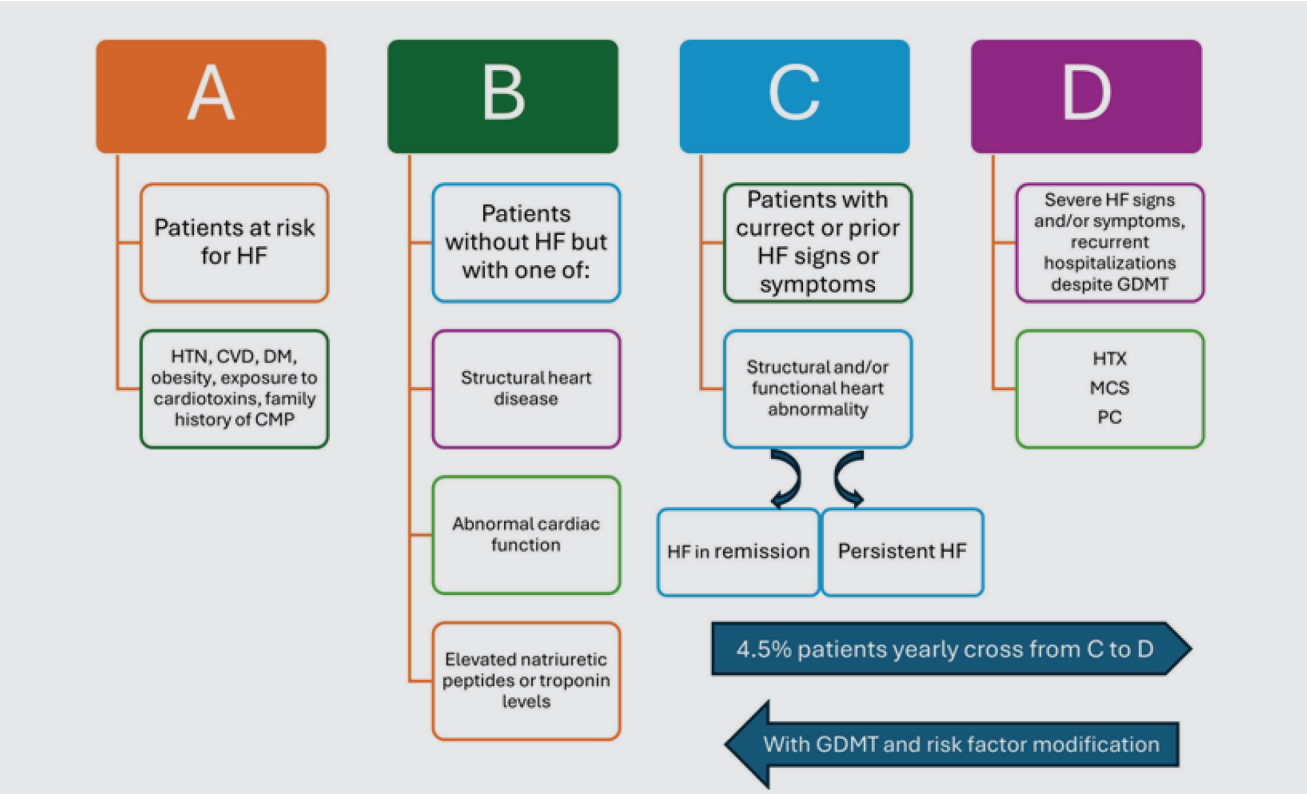

FIGURE 1. Stages of heart failure (adjusted from[10]).
CMP – cardiomyopathy; CVD – cardiovascular disease; DM – diabetes mellitus; GDMT – guideline-directed medical therapy; HF – heart failure; HTN – hypertension; HTX – heart transplantation; MCS – mechanical circulatory support; PC – palliative care

Dunlay *i sur.* proveli su istraživanje koje je uključivalo 6836 bolesnika sa ZS-om, a od kojih je 936 (13,7 %) zadovoljilo kriterije za terminalni stadij. Prosječna dob bolesnika s terminalnim zatajivanjem bila je 77 godina, a 55,5 % bili su muškarci. Reduciranu ejekcijsku frakciju imalo je 42,3 % bolesnika s terminalnim zatajivanjem, umjereno/blago reduciranu 14,3 %, a očuvanu 43,4 % bolesnika. Prevalencija terminalnog ZS-a rasla je s dobi te je bila veća u muškaraca, a medijan preživljenja od trenutka dijagnoze terminalnog stadija do smrti iznosio je 12,2 mjeseci. Pokazalo se da je terminalni stadij ZS-a povezan

Dunlay et al conducted a study that included 6,836 patients with HF, of which 936 (13.7%) met the end-stage criteria. The average age of patients with end-stage HF was 77 years, and 55.5% were men. Only 42.3% of patients with end-stage HF had a reduced ejection fraction, 14.3% had a moderately/mildly reduced ejection fraction and 43.4% had a preserved ejection fraction. The prevalence of end-stage HF increased with age and was higher in men, and the median survival from the moment of end stage diagnosis to death was 12.2 months. End-stage HF was shown to be associated with poor prognosis ir-

s lošom prognozom neovisno o LVEF-u[11]. Prema Kalogeropoulosu *i sur.*, svake godine 4,5 % bolesnika iz stadija C napreduje u stadij D[12].

Simptomi i znakovi ZS-a mogu biti manje ili više tipični i specifični[13]. U uznapredovalome stadiju ZS-a multipli su i više izraženi. Obilježje ZS-a jest retencija vode i natrija, što dovodi do plućne kongestije u ljevostranom i periferne kongestije u desnostranom ZS-u[14]. Najčešći simptomi zatajivanja lijeve klijetke jesu zaduha u naporu, ortopneja i paroksizmalna noćna dispneja. Napredovanjem ZS-a zaduha se počinje pojavljivati i u mirovanju. Bolesnici su često tahikardni i tahipnoični, a oni s teškim zatajivanjem mogu biti i cijanotični. Najčešći simptomi zatajivanja desne klijetke jesu umor, težina u nogama i malaksalost, a znakovi periferni tjestasti edemi, ascites, hepatomegalija i povišen jugularni venski tlak[15]. U bolesnika s terminalnim ZS-om prezentira se specifičan hemodinamski profil koji je karakteriziran visokim tlakom punjenja lijeve klijetke, a dodatno obilježje čini i smanjeni minutni volumen koji rezultira sistemskom hipoperfuzijom. Bendopneja, odnosno pojava dispneje u trenutku kada se bolesnik nagne prema naprijed, smatra se specifičnim simptomom terminalnog ZS-a. S druge strane, hropci koji kao znak mogu upućivati na ZS, odsutni su u više od 80 % bolesnika u terminalnom stadiju[16]. Najčešće kliničke manifestacije bolesnika s terminalnim ZS-om uključuju netoleranciju napora, nenamjeran gubitak težine, rekurentne ventrikularne aritmije, refraktorno volumno opterećenje, hipotenziju te znakove neadekvatne perfuzije koji se pojavljuju unatoč primjeni optimalne terapije[17].

Liječenje uznapredovalog zatajivanja srca

FARMAKOLOŠKA TERAPIJA

Prema smjernicama, terapiju lijekovima koji utječu na prognozu bolesti potrebno je titrirati do maksimalne propisane doze ili maksimalne doze koju bolesnik može tolerirati (**tablica 1**), ali upravo jedan od izazova u liječenju jest činjenica da bolesnici u terminalnom stadiju ZS-a ne toleriraju GDMT zbog hipotenzije ili bubrežne disfunkcije, što je ujedno i prediktor lošijeg ishoda. Redukcija optimalne medikamentne terapije u terminalnom ZS-u srca može prolazno poboljšati simptome, osobito ako se predviđa ili planira uvođenje inotropne potpore i primjena naprednih metoda liječenja. Ako je moguće, potrebno je svakako liječiti specifično i etiologiju ZS-a[1].

LIJEKOVI KOJI MODIFICIRAJU TIJEK BOLESTI

Lijekove koji modificiraju tijek bolesti treba dati svim bolesnicima s HFrEF-om ako nema kontraindikacije. Oni uključuju inhibitore angiotenzin konvertirajućeg enzima (ACEi), blokatore angiotenzinskih receptora (ARB), kombinaciju sakubitril/valsartana (ARNI – inhibitor angiotenzinskog receptora i neprilizina), antagoniste mineralokortikoidnih receptora (MRA) te inhibitore kotransportera natrij glukoza 2 (SGLT2i). Optimalna terapija liječenja HFrEF-a se sastoji se od kombinacije ARNI-ja, beta-blokatora, MRA i SGLT2i. Klasičan pristup postupnom uvođenju svake skupine lijeka do ciljne doze sve se više napušta zbog predugoga vremena od više mjeseci koje je potrebno da se dostigne GDMT, osobito nakon objave rezultata istraživanja *STRONG-HF* s kraja 2022. godine koja je pokazala da je intenzivna titracija svih skupina lijekova u ZS-u nakon stabilizacije sigurna i efikasnija u redukciji novih hospitalizacija zbog ZS-a i smrtnosti[18]. U prilog ovakvomu intenziv-

respective of LVEF[11]. According to Kalogeropoulos et al, every year 4.5% of patients progress from stage C to stage D[12].

Symptoms and signs of HF can be more or less typical and specific[13]. They are multiple and more pronounced in the advanced stage of HF. HF is characterized by the retention of fluid and sodium, which leads to pulmonary congestion in the left-sided, and peripheral congestion in the right-sided HF[14]. The most common symptoms of left ventricular failure are dyspnea during exercise, orthopnea and paroxysmal nocturnal dyspnea. As HF progresses, dyspnea begins to appear even at rest. Patients are often tachycardic and tachypnoic, and those with severe HF may also be cyanotic. The most common symptoms of right ventricular failure are fatigue, heaviness in legs and weakness, and the signs are peripheral pitting edema, ascites, hepatomegaly and increased jugular venous pressure[15]. Patients with end-stage HF present with a specific hemodynamic profile characterized by high left ventricular filling pressure, and an additional feature is the reduced cardiac output resulting in systemic hypoperfusion. Bendopnea, i.e. the dyspnea that happens when the patient bends over, is considered a specific symptom of end-stage HF. On the other hand, rales, which can be a sign of HF, are absent in more than 80% of patients in the end stage[16]. The most common clinical manifestations of patients with end-stage HF include exercise intolerance, unintentional weight loss, recurrent ventricular arrhythmias, refractory volume overload, hypotension and signs of inadequate perfusion that occur despite optimal therapy[17].

Treatment of advanced heart failure

PHARMACOTHERAPY

According to the guidelines, drug therapy that affects the prognosis of the disease must be titrated up to the maximum prescribed dose or the maximum tolerable dose (**Table 1**), but one of the challenges in treatment is the fact that end stage HF patients often do not tolerate GDMT due to hypotension or renal dysfunction, which is also a predictor of a worse outcome. Reduction of optimal drug therapy in end-stage HF can temporarily improve symptoms, especially if introduction of inotropic support and the use of advanced treatment methods is anticipated or planned. If possible, it is necessary to treat specifically the aetiology of heart failure[1].

DRUGS THAT MODIFY THE COURSE OF THE DISEASE

Drugs that modify the course of the disease should be given to all patients with heart failure with reduced ejection fraction (HFrEF) if there are no contraindications. Those include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), sacubitril/valsartan - angiotensin receptor-neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonists (MRA) and sodium-glucose co-transporter 2 inhibitors (SGLT2i). The optimal therapy for the treatment of HFrEF consists of a combination of ARNI, beta blockers, MRA and SGLT2i. The classical approach of gradual introduction of each drug group up to the target dose is increasingly being abandoned because it takes too long, even several months, to reach GDMT, especially after the STRONG-HF study publication at the end of 2022, which showed that intensive titration of all groups of HF drugs early after stabilization is safe and more effective in reducing HF hospitalizations and mortality[18]. This intensive approach is supported by the fact that

TABLE 1. Pharmacotherapy for chronic heart failure with reduced ejection fraction (modified from[1]).

	Starting dose	Target dose
ACEI		
Captopril	6.25 mg tid	50 mg tid
Enalapril	2.5 mg bid	10–20 mg bid
Lisinopril	2.5–5 mg od	20–35 mg od
Ramipril	2.5 mg bid	5 mg bid
Trandolapril	0.5 mg od	4 mg od
ARNI		
Sacubitril valsartan	24/26 mg or 49/51 mg bid	97/103 mg bid
Beta blockers		
Bisoprolol	1.25 mg od	10 mg od
Carvedilol	3.125 mg bid	25 mg bid
Metoprolol	12.5–25 mg od	200 mg od
Nebivolol	1.25 mg od	10 mg od
MRA		
Eplerenone	25 mg od	50 mg od
Spironolactone	25 mg od	50 mg od
SGLT2i		
Dapagliflozin	10 mg od	10 mg od
Empagliflozin	10 mg od	10 mg od
Other drugs		
Candesartan	4 mg od	32 mg od
Losartan	50 mg od	150 mg od
Valsartan	40 mg bid	160 mg bid
Ivabradine	5 mg bid	7.5 mg bid
Vericiguat	2.5 mg od	10 mg od
Digoxin	62.5 µg od	250 µg od
Hydralazine/Isosorbide dinitrate	37.5 mg tid/20 mg tid	75 mg tid/40 mg tid

ACE-I – angiotensin-converting enzyme inhibitor; ARNI – angiotensin receptor-neprilysin inhibitor; bid – bis in die (twice daily); MRA – mineralocorticoid receptor antagonist; od – omne in die (once daily); SGLT2 – sodium-glucose co-transporter 2; tid – ter in die (three times a day)

nom pristupu ide i činjenica kako većina spomenutih lijekova smanjuje morbiditet i mortalitet unutar 30 dana od uvođenja terapije[19]. Postupan i intenzivan pristup liječenju prikazani su na **slici 2**[20].

BETA-BLOKATORI

Beta-blokatori čine jednu od temeljnih terapija ZS-a, ali se samo nekoliko istraživanja usredotočilo na njihovu primjenu u terminalnome stadiju. U istraživanje *COPERNICUS* uključeno je 2289 bolesnika sa znatnom redukcijom ejekcijske frakcije lijeve klijetke (LVEF <25 %) i sa značajnim simptomima (NYHA III. i IV. stupanj) unatoč primjeni optimalne terapije. Bolesnici su randomizirani u dvije skupine, od kojih je jedna primila karvediol, a druga placebo te je zabilježena znatna redukcija mortaliteta u bolesnika koji su primili karvediol[21]. S obzirom na nedostatak dokaza o utjecaju beta-blokatora na

most of these drugs reduce morbidity and mortality within 30 days of therapy introduction[19]. Gradual and intensive approach to treatment is shown in **Figure 2**[20].

BETA BLOCKERS

Beta blockers are one of the basic therapies for HF, but only a few studies have focused on their use in the end stage HF. The COPERNICUS study included 2,289 patients with significantly reduced left ventricular ejection fraction (LVEF <25%) and significant symptoms (NYHA class III and IV) despite the use of optimal therapy. The patients were randomized into two groups: one received carvediol and the other placebo. A significant reduction in mortality was recorded in patients who received carvediol[21]. Given the lack of evidence on the impact of beta blockers on the quality of life in patients with end-stage HF, their use is recommended in combination with

FIGURE 2. Heart failure optimal therapy optimisation – A) conventional; B) intensified (adjusted from[23]).
ACE-I – angiotensin-converting enzyme inhibitor; ARB – angiotensin receptor blocker; ARNI – angiotensin receptor-neprilysin inhibitor; BB – beta blocker; GDMT – guideline-directed medical therapy; MRA – mineralocorticoid receptor antagonist; SGLT2 – sodium-glucose co-transporter 2

kvalitetu života bolesnika s terminalnim zatajivanjem, njihova se primjena preporučuje u kombinaciji s drugim lijekovima koji modificiraju tijek bolesti. Također, terapija beta-blokatorima preporučena je za sve bolesnike u terminalnome stadiju s uvođenjem niske doze i posljedične titracije, odnosno s 50 %-tnim povećanjem doze svaka 2 – 4 tjedna. U liječenju prednost imaju lijekovi s najmanjim hipotenzivnim učinkom poput bisoprolola i metoprolola s produljenim oslobađanjem[16].

MODULATORI RENIN-ANGIOTENZINSKOG SUSTAVA

U istraživanju *PARADIGM-HF* sudjelovala su 8842 bolesnika s optimiranom terapijom i reduciranom ejekcijskom frakcijom te su klasificirani kao NYHA II. – IV., a <1 % bolesnika klasificirano je kao NYHA IV. stupnja. Bolesnici su randomizirani u skupine od kojih je jedna skupina primila sakubitril/valsartan, a druga enalapril uz drugu terapiju za ZS. U skupini koja je primila sakubitril/valsartan zabilježena je redukcija u broju hospitalizacija za 21 % i redukcija mortaliteta od 20 %[22].

U istraživanju *LIFE* uspoređivao se učinak sakubitril/valsartana nasuprot valsartanu u bolesnika klasificiranih kao NYHA IV. stupnja, s LVEF-om od ≤35 % i s povišenim vrijednostima NT-proBNP-a. Rezultati spomenutog istraživanja pokazali su da nije bilo statističke razlike u primjeni sakubitril/valsartana i valsartana u obliku redukcije vrijednosti NT-proBNP-a[23].

Smatra se da je sakubitril/valsartan potrebno primjenjivati u liječenju terminalnog ZS-a, ali primjenu otežava činjenica da bolesnici u teminalnome stadiju i s reduciranom ejekcijskom frakcijom slabije toleriraju veće doze. Preporučena je početna doza 24/26 mg dvaputa na dan te ju je potrebno postupno titrirati tako da se svaka 2 tjedna dnevna doza povisi dvostruko do ukupno dvaputa 97/103 mg[16,24]. Sakubitril/valsartan zasad je, prema smjernicama, u drugoj liniji liječenja,

other drugs that modify the course of the disease. Furthermore, beta blocker therapy is recommended for all patients in the end stage HF starting with a low dose and subsequent titration, i.e. with a 50% dose increase every 2–4 weeks. Beta blockers with the least hypotensive effect, such as bisoprolol and metoprolol with prolonged release, are preferred[16].

MODULATORS OF THE RENIN-ANGIOTENSIN SYSTEM

The PARADIGM-HF study included 8,842 patients with optimal therapy and reduced ejection fraction; they were classified as NYHA class II–IV and <1% of patients were classified as NYHA class IV. The patients were randomized into groups, one of which received sacubitril/valsartan, and the other enalapril with other HF therapy. The group that received sacubitril/valsartan showed a reduction in the number of hospitalizations by 21% and a reduction in mortality by 20%[22].

The LIFE study compared the effect of sacubitril/valsartan versus valsartan in patients classified as NYHA class IV, with LVEF ≤35% and elevated NT-proBNP level. The results of this study showed that there was no statistical difference in the use of sacubitril/valsartan and valsartan in terms of NT-proBNP reduction[23].

It is considered that sacubitril/valsartan should be used in the treatment of end-stage HF, but its application should be carefully implemented as patients in the end stage HF tolerate higher doses less. The recommended starting dose is 24/26 mg twice a day and it should be gradually titrated so that every 2 weeks the daily dose is doubled to a total of 97/103 mg twice a day[16,24]. According to the guidelines, sacubitril/valsartan is currently in the second line of treatment, i.e. it is used in patients with HFrEF if ACEi or ARB cannot con-

tj. primjenjuje se u bolesnika s HFrEF-om ako ACEi ili ARB ne postižu kontrolu simptoma i bolesti. Vrlo je važno, kada se uvodi sakubitril/valsartan, da bolesnici koji su bili na ACEi-ju imaju vrijeme od 36 sati između prestanka uzimanja ACEi-ja i početka uzimanja ARNI-ja[1].

ANTAGONISTI MINERALOKORTIKOIDNIH RECEPTORA

Najučinkovitiju strategiju za kompletnu inhibiciju RAAS-a čini kombinacija ARNI-a i MRA-a[16].

U istraživanju RALES primjena spironolaktona rezultirala je smanjenim mortalitetom i hospitalizacijama u bolesnika s terminalnim ZS-om. Učinkovitost primjene spironolaktona zabilježena je i u bolesnika s oštećenjem renalne funkcije ili umjerene hiperkalemije[16,25].

Međutim, nema dovoljno dokaza o definitivnom učinku na kvalitetu života, ali unatoč tome preporučuje se primjena spironolaktona u svih bolesnika s terminalnim zatajivanjem i razinom serumskog kalija <5 mEq/L. Preporučeno je postupno uvođenje niske doze spironolaktona s titracijom terapije nakon 2 – 4 tjedna kako bi se postigla ciljna doza od 50 mg na dan, a usto je potrebno redovito kontrolirati serumsku razinu kalija. Ako je razina kalija >6 mEq/L nakon uvođenja MRA-a, preporučuje se ukidanje svih lijekova koji su u interakciji s RAAS-om[16]. Eplerenon, kao selektivniji MRA od spironolaktona, bolji je izbor zbog manje stope nuspojava.

SGLT2 INHIBITORI

SGLT2i su novi lijekovi u liječenju kroničnog ZS-a. Inicijalno razvijeni kao hipoglikemici, njihov pozitivan učinak na velike kardiovaskularne (KV) ishode u ZS-u, bez obzira na prisutnost šećerne bolesti, istraživanja su dokazala potkraj prošloga desetljeća: *EMPEROR – Reduced* za empagliflozin i *DAPA-HF* za dapagliflozin[26,27]. SGLT2i su jedina skupina lijekova koja utječe na prognozu ZS-a u cijelome spektru ejekcijske frakcije uz dobar sigurnosti profil, mnogostruke povoljne učinke i jednostavno doziranje. Jasni dokazi za korist u ZS-u s blago reduciranom i očuvanom ejekcijskom frakcijom postoje za empagliflozin (*EMPEROR-Preserved*) i dapagliflozin (*DELIVER*)[28,29]. Mehanizmi kojim SGLT2i djeluju na poboljšanje bolesti različiti su i još nedovoljno istraženi. Osim kontrole glikemije, neki od njih uključuju natriurezu, smanjenje endotelne disfunkcije, smanjenje proizvodnje proupalnih citokina, smanjenje oksidativnoga stresa, regulacija hiperuricemije, hiperfiltracije u bubrezima, smanjenje intraglomerularnog tlaka i albuminurije.

Kada se započne terapija RAAS inhibitorima, s ARNI ili SGLT2i može se očekivati prolazno pogoršanje bubrežne funkcije te se ne treba žuriti s ukidanjem spomenutih lijekova osobito ako su porast kreatinina <50 % i apsolutna vrijednost je <266 µmol/L ili je pad glomerularne filtracije <10 % i vrijednost apsolutno >25 mL/min/1,73 m^2[1].

DIURETICI I LIJEČENJE KONGESTIJE

Poboljšanje simptoma kongestije u bolesnika s terminalnim ZS-om može se postići primjenom diuretika u velikoj dozi ili kontinuiranoj infuziji, a dekongestija se smatra značajnim prognostičkim čimbenikom preživljenja. Blago i prolazno povišenje kreatinina u liječenju akutnog ZS-a nije povezano s lošijim ishodom ako je bolesnik bez kongestije. Međutim, klinički tijek terminalnog ZS-a obilježen je razvojem kardi-

trol the symptoms and disease. When introducing sacubitril/valsartan, it is very important that patients who were on ACEi have a wash out period of 36 hours between stopping ACEi and starting ARNI[1].

MINERALOCORTICOID RECEPTOR ANTAGONISTS

The most effective strategy for complete RAAS inhibition is the combination of ARNI and MRA[16].

In the RALES study, the use of spironolactone resulted in reduced mortality and hospitalization in patients with end-stage HF. The effectiveness of the use of spironolactone has also been recorded in patients with impaired renal function or moderate hyperkalemia[16,25].

However, there is insufficient evidence of a definitive effect on quality of life, but spironolactone is nonetheless recommended for all patients with end-stage HF and a serum potassium level < 5 mEq/L. A gradual introduction of a low dose spironolactone with titration of therapy after 2–4 weeks was recommended in order to reach the target dose of 50 mg per day. Additionally, it is necessary to regularly control serum potassium level. If the potassium level is > 6 mEq/L after MRA introduction, it is recommended to discontinue all drugs that interact with RAAS[16]. Eplerenone, as a more selective MRA than spironolactone, is a better choice due to a lower side effect rate.

SGLT2 INHIBITORS

SGLT2i are new drugs in the treatment of chronic HF. Initially developed as hypoglycemics, their positive effect on major cardiovascular (CV) outcomes in HF, regardless of the presence of diabetes, was proven by two studies at the end of the last decade: EMPEROR-Reduced for empagliflozin and DAPA-HF for dapagliflozin[26,27]. SGLT2i are the only group of drugs that affects HF prognosis across the ejection fraction spectrum with a good safety profile, multiple beneficial effects and simple dosing. There is clear evidence of benefit in HF with slightly reduced and preserved ejection fraction for empagliflozin (EMPEROR-Preserved) and dapagliflozin (DELIVER)[28,29]. The mechanisms by which SGLT2i act to improve the disease are multiple and still insufficiently investigated. In addition to glycemic control, some of them include natriuresis, reduction of endothelial dysfunction, reduction of pro-inflammatory cytokine production, reduction of oxidative stress, regulation of hyperuricemia and hyperfiltration in kidneys, reduction of intraglomerular pressure and albuminuria.

When starting therapy with RAAS inhibitors, ARNI or SGLT2i, a temporary deterioration of renal function can be expected so there is no need to rush to discontinue these drugs, especially if the increase in creatinine is < 50% and the absolute value is < 266 µmol/L or if the glomerular filtration fall is < 10% and absolute value > 25 mL/min/1.73 m^2[1].

DIURETICS AND TREATMENT OF CONGESTION

Improvement of the symptoms of congestion in patients with end-stage HF can be achieved by using diuretics in high dose or continuous infusion, and decongestion is considered as a significant prognostic factor of survival. A mild and transient increase in creatinine in the treatment of acute HF is not associated with a worse outcome if the patient shows no signs of congestion. However, the clinical course of end-stage HF is characterized by the development of cardiorenal syndrome and resistance to diuretics, which further complicates treat-

orenalnog sindroma i rezistencije na diuretike, što dodatno otežava liječenje. Potrebno je progresivno povećavati dozu zbog rezistencije kako bi se ostvario željeni učinak, a jedan od glavnih mehanizama nastanka rezistencije jest remodeliranje nefrona zbog produljena liječenja diureticima. U slučaju nastanka rezistencije prvu terapijsku opciju čini povećanje oralne doze diuretika Henleove petlje, a bolesnici s neadekvatnim odgovorom trebaju primiti intravenske diuretike s početnom dozom većom od oralne. Ako se primijenjenom terapijom nije postigla odgovarajuća diureza, daljnje liječenje uključuje kombinaciju diuretika Henleove petlje i drugih diuretika. Bitno je istaknuti da ta kombinacija može rezultirati hipokalemijom i hiponatremijom. U slučaju da primijenjenom terapijom nisu ostvaren željeni ishod i adekvatna diureza, potrebno je razmotriti ultrafiltraciju kao sljedeću terapijsku opciju. Potrebno je odrediti brzinu ultrafiltracije koja se mora održavati ili smanjivati jer uklanjanje tekućine rezultira smanjenim kapilarnim punjenjem i ne preporučuje se brzina >250 mL/h[9,16,30,31]. Rezistencija na diuretike i pogoršanje bubrežne funkcije indikatori su terminalnog zatajivanja i potrebe za naprednim liječenjem[32,33].

OSTALI LIJEKOVI U KRONIČNOM ZATAJIVANJU SRCA

Za pojedine skupine bolesnika dolazi u obzir i primjena nekih drugih lijekova. Ivabradin – blokator I_f kanala u sinoatrijskom čvoru, može se dati bolesnicima sa ZS-om koji su u sinusnom ritmu frekvencije >70/min, a ne mogu tolerirati beta-blokator. Digoksin - antiaritmik i inotrop, dolazi kao terapijska opcija u bolesnika s HFrEF-om koji imaju trajnu fibrilaciju atrija neregulirane frekvencije[1]. Primjena željezo-hidroksimaltoze intravenski u bolesnika s nedostatkom željeza sigurna je i poboljšava simptome neovisno o tome imaju li ili nemaju anemiju[34]. Zbog navedenog, preporučuje se rutinska provjera ferograma u bolesnika sa ZS-om pri kontrolama.

Vericiguat je nov lijek kao opcija u liječenju ZS-a. Stimulator je topljive gvanilat ciklaze (sGC) koji povećava proizvodnju dušikova oksida. Svoj učinak ostvaruje izravnim stimuliranjem sGC-a tako da se veže na vezno mjesto neovisno o dušikovu oksidu, te senzibilizira sGC na endogeni dušikov oksid. Time stabilizira vezanje dušikova oksida za vezno mjesto. U istraživanje *VICTORIA* uključeni su bolesnici s pogoršanjem simptoma i HFrEF-om koji su nedavno bili hospitalizirani ili primili intravensku diuretsku terapiju. U ispitivanje je uključeno 5050 bolesnika s kroničnim ZS-om, NYHA-om II. – IV. stupnja, LVEF-om <45% i povišenim vrijednostima natriuretskih peptida unutar 30 dana od randomizacije. Bolesnici su podijeljeni u dvije skupine, od kojih je jedna primila vericiguat, a druga placebo uz GDMT. Kombinirani primarni ishod bio je smrt zbog KV uzroka ili je prva hospitalizacija vezana uz ZS. Rezultati istraživanja pokazali su pojavljivanje primarnog ishoda u 35,5 % bolesnika koji su primili vericiguat u odnosu na 38,5 % bolesnika koji su primili placebo. Hospitalizacija zbog zatajivanja zabilježena je u 27,4 % bolesnika koji su primili vericiguat, u odnosu prema 29,6 % bolesnika na placebu (HR 0,90; 95 % CI, 0,81 – 1 ,00). Također je zabilježena i manja incidencija KV smrti u grupi koja je primila vericiguat. Međutim, simptomatska se hipotenzija pojavila u 9,1 % bolesnika na terapiji vericiguatom u usporedbi s 7,9 % ispitanika na placebu, a sinkopa u 4 % bolesnika koji su primili vericiguat u odnosu prema 3,5 % onih na placebu. Dakle, pokazalo se da vericiguat smanjuje incidenciju smrti zbog KV uzroka i hospitalizacija zbog zatajivanja srca, ali povećava incidenciju simptomatske hipotenzije.

ment. In order to achieve the desired effect, it is necessary to progressively increase the dose due to resistance, and one of the main mechanisms of resistance is remodelling of the nephron due to prolonged treatment with diuretics. In the case of resistance, the first therapeutic option is to increase the oral dose of loop diuretics, and patients with an inadequate response should receive intravenous diuretics with an initial dose higher than the oral one. If adequate diuresis is not achieved with the applied therapy, further treatment includes a combination of loop diuretics and other diuretics. It is important to point out that this combination can result in hypokalemia and hyponatremia. If the applied therapy did not achieve the desired outcome and adequate diuresis, it is necessary to consider ultrafiltration as the next therapeutic option. It is necessary to determine the speed of ultrafiltration. Due to reduced capillary refill, ultrafiltration speed >250 mL/h is not recommended[9,16,30,31]. Resistance to diuretics and deterioration of renal function are indicators of end-stage HF and the need for advanced treatment[32,33].

OTHER DRUGS IN CHRONIC HEART FAILURE

For certain groups of patients, the use of some other drugs is also considered. Ivabradine – an I_f channel blocker in the sinoatrial node can be given to HF patients who are in sinus rhythm with heart rate >70/min and who cannot tolerate beta blockers. Digoxin, an antiarrhythmic and inotrope, is a therapeutic option in patients with HFrEF who have persistent tachyarrythmic form of atrial fibrillation[1]. Administration of iron-hydroxymaltose intravenously in iron-deficient patients is safe and improves symptoms regardless of presence of anaemia[34]. Therefore, a routine check for iron deficiency in HF patients is recommended.

Vericiguat is a new drug as an option in the treatment of HF. It is a soluble guanylate cyclase (sGC) stimulator which increases nitric oxide production. It achieves its effect by directly stimulating sGC independently of nitric oxide and sensitises sGC to endogenous nitric oxide. This stabilises the binding of nitric oxide to the binding site. The VICTORIA study included patients with worsening symptoms and HFrEF who had recently been hospitalized or who had received intravenous diuretic therapy. The study included 5,050 patients with chronic heart failure, NYHA class II–IV, LVEF < 45% and elevated natriuretic peptide level within 30 days before randomization. The patients were divided into two groups, one of which received vericiguat and the other placebo in addition to GDMT. The primary composite endpoint was CV death or first HF hospitalization. The results of the study showed the occurrence of the primary endpoint in 35.5% of patients who received vericiguat compared to 38.5% of patients who received placebo. HF hospitalization was recorded in 27.4% of patients who received vericiguat, compared to 29.6% of patients on placebo (HR 0.90; 95% CI, 0.81–1.00). Furthermore, a lower incidence of CV death was recorded in the group that received vericiguat. Symptomatic hypotension occurred in 9.1% of patients on vericiguat versus 7.9% on placebo, and syncope occurred in 4% of patients receiving vericiguat versus 3.5% on placebo. Thus, vericiguat has been shown to reduce the incidence of CV death and HF hospitalization[35]. It has been shown that the use of vericiguat will reduce the primary composite endpoint and its components in patients with NT-proBNP level <8000 pg/mL and that vericiguat has the most significant therapeutic effect at NT-proBNP level <4000 pg/mL[36]. Accord-

pitalizaciju bolesnika vezanu uz ZS[35]. Pokazalo se također da će se primjenom vericiguata reducirati kombinirani primarni ishod i njegove komponente u bolesnika čije su vrijednosti NT-proBNP-a <8000 pg/mL i da vericiguat ima najznačajniji terapijski učinak pri vrijednostima NT-proBNP-a <4000 pg/mL[36]. Prema smjernicama, vericiguat se može razmotriti kao dodatak standarnoj terapiji za liječenje HFrEF-a, no uz razinu preporuke IIb[1].

INOTROPNA POTPORA

Inotropni lijekovi pojačavaju kontraktilnost srca i, posljedično tomu, povećavaju i minutni volumen, a imaju i vazodilatacijski ili vazokonstrikcijski učinak ovisno o specifičnom lijeku i dozi. Uporabljuju se u težim manifestacijama ZS-a, pokatkad uz usporednu potrebu za uvođenjem i vazokonstriktora. Inotropi mogu poboljšati hemodinamske parametre i funkciju ciljnih organa u bolesnika s terminalnim zatajivanjem, a primjenjuju se u svrhu olakšanja simptoma ili kao terapija premoštenja do transplantacije ili ugradnje MCS uređaja. Međutim, rutinska se primjena ne preporučuje jer inotropna potpora nije povezana s poboljšanjem prognoze, nego je u nekim slučajevima može čak i pogoršati. Nadalje, nije preporučena ni dugoročna primjena u bolesnika koji čekaju transplantaciju srca, ali se može dugoročno primjenjivati kao palijativna mjera u bolesnika bez drugih terapijskih opcija[9,31].

Inotropni intravenski lijekovi koji se uporabljuju uključuju beta-adrenergičke agoniste, inhibitore fosfodiesteraze 3 i senzibilizatore kalcija. Najčešće se primjenjuju dobutamin, milrinon i levosimedan koji će se detaljnije opisati u nastavku teksta, a vodeći je princip primjena najmanje doze u najkraćemu vremenu potrebnom za postizanje kliničkog učinka[33,37]. Prema metaanalizi, dugoročna primjena infuzije inotropa rezultirala je poboljšanjem NYHA stupnja u bolesnika s terminalnim zatajivanjem i reduciranom ejekcijskom frakcijom, međutim, nije zabilježena značajna statistička razlika u mortalitetu s obzirom na kontrole. Ograničeni su dokazi o rizicima i prednostima primjene infuzije inotropa u nehospitaliziranih bolesnika s terminalnim zatajivanjem[38].

Pokazalo se da je primjena inotropnih lijekova u obliku intravenske infuzije kod kuće znatan teret za bolesnikovu obitelj, a ujedno može povećati rizik od smrti zbog nastupa aritmije. Pritom se postavlja etička dvojba vezana uz poboljšanje kvalitete života i skraćenja njegova trajanja. Potrebno je donijeti zajedničku odluku o uvođenju kontinuirane inotropne potpore u bolesnika koji nisu kandidati za transplantaciju i ugradnju mehaničke potpore lijevoj klijetci (LVAD-a)[39]. Tijekom odlučivanja o kontinuiranoj primjeni infuzije inotropa nužno je razmotriti potrebu za olakšanjem simptoma, kao i bolesnikove želje, međutim, većina će bolesnika biti rehospitalizirana nakon uvođenja kontinurane inotropne terapije[40]. Cilj primjene inotropne potpore u bolesnika s terminalnim ZS-om koji su za palijativno liječenje trebao bi biti poboljšanje kvalitete života i funkcijskog kapaciteta[30].

DOBUTAMIN

Dobutamin je beta-adrenergički agonist koji povećava minutni volumen srca i smanjuje plućni kapilarni tlak, a njegova je primjena preporučena u liječenju bolesnika sa smanjenim minutnim volumenom i smanjenom perfuzijom organa. Unatoč teoretskoj potencijalnoj učinkovitosti dobutamina u liječenju terminalnog zatajivanja, mali je broj istraživanja koji

ing to the guidelines, vericiguat can be considered as an adjunct to standard HFrEF therapy, but with a recommendation level of IIb[1].

INOTROPIC SUPPORT

Inotropic drugs increase heart contractility and consequently cardiac output as well. They also have a vasodilating or vasoconstricting effect depending on the specific drug and dose. They are used in severe HF manifestations, sometimes with the parallel need to give vasoconstrictors. Inotropes can improve hemodynamic parameters and end organ function in patients with end-stage HF, and are used to relieve symptoms or as bridge therapy until transplantation or MCS device implantation. However, routine use is not recommended because inotropic support is not associated with improving the prognosis, and in some cases can even worsen it. Furthermore, long-term use is also not recommended in patients waiting for a heart transplant, but it can be used in the long term as a palliative measure in patients without other therapeutic options[9,31].

Used inotropic intravenous drugs include beta-adrenergic agonists, phosphodiesterase 3 inhibitors and calcium sensitizers. The most commonly used inotropes are dobutamine, milrinone and levosimedan, which will be described in more detail below. Administration principle is to give the smallest effective dose in the shortest time necessary to achieve a clinical effect[33,37]. According to a meta-analysis, long-term use of inotrope infusion resulted in an improvement of the NYHA class in patients with end-stage HF and reduced ejection fraction; however, no significant statistical difference in mortality compared to controls was recorded. There is limited evidence of the risks and benefits of inotrope infusion in non-hospitalized patients with end-stage HF[38].

It has been shown that the use of inotropes in the form of intravenous infusion at home represents a significant burden for the patient's family and at the same time can increase the risk of death due to arrhythmias. This raises an ethical dilemma related to improving the quality of life and shortening the duration of life. It is necessary to make a joint decision on them introduction of continuous inotropic support in patients who are not eligible for transplantation and left ventricular assist device (LVAD) implantation[39]. When deciding on the continuous use of inotrope infusion, it is necessary to consider the need for symptom relief as well as the patient's wishes. However, most patients will be rehospitalized after the introduction of continuous inotrope therapy[40]. The goal of applying inotropic support in patients with end-stage HF in palliative treatment should be to improve the quality of life and functional capacity[30].

DOBUTAMINE

Dobutamine is a beta-adrenergic agonist that increases cardiac output and decreases pulmonary capillary pressure. Its use is recommended in the treatment of patients with reduced cardiac output and reduced organ perfusion. Despite the potential effectiveness of dobutamine in the treatment of end-stage HF, there is a small number of studies that addressed the effect of dobutamine in patients with end-stage HF[30,33].

In the FIRST study, it was reported that continuous intravenous dobutamine was associated with a higher 6-month mortality rate in patients with end-stage HF[41].

govori o djelovanju dobutamina u bolesnika s terminalnim zatajivanjem[30,33].

U istraživanju *FIRST* zabilježeno je da je kontinuirana intravenska primjena dobutamina bila povezana s većom stopom 6-mjesečnog mortaliteta u bolesnika s terminalnim ZS-om[41].

MILRINON

Milrinon je inhibitor fosfodiesteraze 3 koji povećava unutarstaničnu koncentraciju kalcija te ima inotropni i vazodilatacijski učinak. Vazodilatacijski učinak može rezultirati hipotenzijom i dodatnom hipoperfuzijom u bolesnika koji su već hipotenzivni. Unatoč tomu, milrinon je terapija izbora za bolesnike sa sistemskom i plućnom hipertenzijom te smanjenim minutnim volumenom te onima kojima treba inotropna potpora zbog pogoršanja, a beta-receptori su blokirani ranijom primjenom beta-blokatora[33,37].

Istraživanje *OPTIME-CHF* uključivalo je 951 bolesnika randomiziranog u grupu koja je primila 48-satnu infuziju milrinona i grupu koja je primila placebo, a svrha je bila utvrditi može li kratkoročna terapija milrinonom poboljšati klinički ishod u bolesnika hospitaliziranih zbog egzacerbacije kroničnog ZS-a. Rezultati su pokazali da nije bilo značajne razlike u mortalitetu i rehospitalizacijama, no primjena milrinona bila je znatno povezana s većom incidencijom hipotenzije i nastankom aritmija[42].

LEVOSIMENDAN

Levosimendan pojačava osjetljivost miocita za kalcij, ali nema utjecaj na njegovu unutarstaničnu koncentraciju. Aktivira ATP-ovisne kalijeve kanale glatkih mišića i mitohondrija te posljedično uzrokuje sistemnu i plućnu vazodilataciju, a ujedno je i kardioprotektivan. Konvencionalni inotropi poput beta-adrenergičkih agonista i inhibitora fosfodiesteraze 3 povećavaju koncentraciju intracelularnog kalcija i posljedično njihova primjena nosi veći rizik od ventrikularne aritmije. S obzirom na produljeni učinak čak i do 14 dana, može se rabiti kao periodična infuzija održavanja za bolesnike s terminalnim ZS-om[16].

U istraživanju *PERSIST* randomizirano je 307 bolesnika klasificiranih kao NYHA III. b – IV. u dvije skupine, od kojih je jedna primila levosimendan, a druga placebo. Rezultati su pokazali poboljšanje kvalitete života i smanjenje vrijednosti NT-proBNP-a u bolesnika koji su primili levosimendan[43].

S druge strane, u istraživanje *LevoRep* uključeno je 120 bolesnika s terminalnim ZS-om te su podijeljeni u dvije skupine, od kojih je jedna primila levosimendan, a druga placebo. Rezultati su pokazali da nije bilo znatnog poboljšanja funkcijskog kapaciteta ili kvalitete života u bolesnika u terminalnom stadiju koji su primili levosimendan[44].

U istraživanju *LION-HEART* 69 bolesnika s terminalnim zatajivanjem randomizirano je u skupine u kojoj je jedna primila placebo, a druga levosimendan u dozi od 0,2 µg/kg/min (tijekom 6 sati, svaka 2 tjedna, kroz 12 tjedana). U grupi koja je primila levosimendan zabilježena je redukcija koncentracije NT-proBNP-a u plazmi i manja učestalost hospitalizacije u usporedbi s bolesnicima koji su primili placebo[45]. Smatra se da bolesnici dobro toleriraju infuzije levosimendana i da ima dobar terapijski učinak u selektiranih bolesnika s terminalnim ZS-om kao terapija održavanja u bolesnika koji nisu kandidati za transplantaciju srca i ugradnju LVAD-a[46].

MILRINONE

Milrinone is a phosphodiesterase 3 inhibitor that increases intracellular calcium concentration and has an inotropic and vasodilating effect. The vasodilating effect may result in hypotension and additional hypoperfusion in patients who are already hypotensive. Nevertheless, milrinone is the therapy of choice for patients with systemic and pulmonary hypertension and reduced cardiac output, and for those who need inotropic support due to the aggravation of disease and beta receptors have been blocked by the earlier use of beta blockers[33,37].

The OPTIME-CHF study included 951 patients randomized to receive 48 hours of intravenous milrinone therapy or placebo, and the aim was to determine whether short-term milrinone therapy could improve clinical outcomes in patients hospitalized for exacerbation of chronic HF. The results showed that there was no significant difference in mortality and rehospitalization, but the use of milrinone was significantly associated with a higher incidence of hypotension and the occurrence of arrhythmias[42].

LEVOSIMENDAN

Levosimendan enhances the sensitivity of myocytes to calcium, but has no effect on intracellular calcium concentration. It activates ATP-sensitive potassium channels of smooth muscles and mitochondria and consequently causes systemic and pulmonary vasodilation. It is also cardioprotective. Conventional inotropes such as beta-adrenergic agonists and phosphodiesterase 3 inhibitors increase the concentration of serum calcium and consequently their use entails a higher risk of ventricular arrhythmias. Given the prolonged effect, even up to 14 days, it can be used as a periodic maintenance infusion for patients with end-stage HF[16].

In the PERSIST study, 307 patients classified as NYHA IIIb–IV were randomized in two groups, one of which received levosimendan and the other placebo. The results showed an improvement in quality of life and a decrease in NT-proBNP level in patients who received levosimendan[43].

On the other hand, the LevoRep study included 120 patients with end-stage HF randomized to receive levosimendan or placebo. The results showed that there was no significant improvement in functional capacity or quality of life in patients in the end stage who received levosimendan[44].

In the LION-HEART study, 69 patients with end-stage HF were randomized into two groups to receive placebo or levosimendan at a dose of 0.2 µg/kg/min (over 6 hours, every 2 weeks for 12 weeks). In the group that received levosimendan, there was a reduction in the plasma concentration of NT-proBNP and a lower frequency of hospitalization compared to patients who received placebo[45]. It is considered that levosimendan infusions are well tolerated by patients and that it has a good therapeutic effect in selected patients with end-stage HF as maintenance therapy in patients who are not eligible for heart transplantation and LVAD implantation[46].

Upućivanje bolesnika u specijalizirane centre

Napredno liječenje bolesnika s terminalnim ZS-om uključuje transplantaciju srca i ugradnju MCS-a, a pravodobno upućivanje u specijalizirane centre za napredno liječenje (AHFC) jedan je od preduvjeta za uspješan ishod[9,47].

Važno je istaknuti da prekasno upućivanje može rezultirati brojnim neželjenim posljedicama koje znatno utječu na ishod liječenja. Naime, bolesnici se prekasnim upućivanjem mogu izložiti većem riziku od pogoršanja stanja i nastanka kardiogenog šoka, a može nastupiti i ireverzibilna disfunkcija organa poput progresivnoga bubrežnog i jetrenog zatajivanja, zbog čega bolesnik možda neće biti kandidati za transplantaciju srca i ugradnju LVAD-a[47].

Prvi korak u donošenju odluke za upućivanje u specijalizirane centre jest prepoznavanje bolesnika s kliničkom slikom terminalnog zatajivanja, zbog čega je preporučeno procijeniti progresiju bolesti na svakome kontrolnom pregledu. Klinički pokazatelji koji upućuju na progresiju uključuju primjenu inotropne potpore, NYHA III. ili IV. stupnja, perzistentno povišene natriuretske peptide, disfunkciju ciljnih organa, LVEF <20 %, učestale defibrilacijske šokove, više od jedne hospitalizacije u posljednjih 12 mjeseci, perzistentne edeme, konstantno niski arterijski tlak te netoleranciju GDMT-a[9,47,48].

Postoje određeni kriteriji prema kojima se trijažiraju i određuju kandidati za transplantaciju i ugradnju MCS-a, međutim, nisu dostupne točno određene smjernice i kriteriji prema kojima bi se bolesnici pravodobno uputili u AHFC[29,31]. Prepoznavanje bolesnika kojima je potrebno napredno liječenje dodatno otežava nepredvidiva klinička slika ZS-a jer u nekim slučajevima nastupa nagla progresija bolesti[49,50].

Prema HFA-ESC-u, predloženi su kriteriji na temelju kojih bi se bolesnici upućivali u AHFC, a uključuju kliničke, laboratorijske i slikovne parametre te modele procjene rizika prikazanih u **tablici 2**[9].

Važno je istaknuti da više od dviju hospitalizacija u posljednjih 12 mjeseci upućuju na vrlo visok rizik od lošeg ishoda, odnosno, na taj se način mogu identificirati bolesnici s jednogodišnjim mortalitetom većim od 40 %. Idealno vrijeme za upućivanje u mjerodavne centre jest razdoblje u kojemu još uvijek nije nastupilo ireverzibilno oštećenje ciljnih organa, a klinička je slika u skladu s terminalnim stadijem ili se on u skorijemu vremenu može anticipirati[47].

Prema istraživanju koje su proveli Herr *i sur.*, u trenutku upućivanja u tercijarni centar 51,5 % bolesnika imalo je LVEF <20 %, a njih 74,5 % bilo je ovisno o inotropnoj potpori ili im je ugrađen privremeni MCS uređaj. Najveći broj bolesnika upućen je zbog pogoršanja zatajivanja definirana progresivnim simptomima, netolerancijom terapije i hipotenzijom. Ostali uzroci upućivanja uključivali su hospitalizacije, primjenu inotropne potpore i kardiogeni šok. Za transplantaciju srca evaluirano je 78,3 %, a za ugradnju MCS-a 76,5 % bolesnika. Međutim, većina bolesnika nije bila kandidat za transplantaciju, a najčešći su razlozi bili teško bolesnikovo stanje zbog disfunkcije ciljnih organa ili pridruženih komorbiditeta, a dodatno su se istaknuli i psihosocijalni razlozi. Nijedna metoda naprednog liječenja nije bila ponuđena u 37,4 % bolesnika[51].

Lund *i sur.* proveli su istraživanje o probiru kandidata za napredno liječenje u bolesnika s postojećom resinkronizacij-

Referring patients to specialised centres

Advanced treatment of end-stage HF includes heart transplantation and MCS implantation, and timely referral to specialised advanced heart failure centres (AHFC) is one of the prerequisites for a successful outcome[9,47].

It is important to emphasize that too late referral can result in numerous unwanted consequences that significantly affect the outcome of treatment. Namely, by being referred to specialised centres too late, patients may be exposed to a greater risk of the deterioration of the condition and cardiogenic shock occurrence. Irreversible organ dysfunction such as progressive renal and hepatic failure may occur, as a result of which the patient may not be eligible for heart transplantation or LVAD implantation[47].

The first step towards making a decision to refer a patient to a specialised centre is identifying patients with a clinical picture of end-stage HF, which is why it is recommended to assess the progression of the disease at each follow-up examination. Clinical indicators suggestive of progression include the use of inotropic support, NYHA class III or IV, persistently elevated natriuretic peptides, end organ dysfunction, LVEF <20%, frequent defibrillation shocks, more than one hospitalization in the last 12 months, persistent edema, persistently low arterial pressure and GDMT intolerance[9,47,48].

There are certain criteria according to which candidates for transplantation and MCS implantation are triaged and identified. However, there are no exact guidelines and criteria according to which patients would be timely referred to an AHFC[29,31]. Identification of patients who need advanced treatment is further complicated by the unpredictable clinical picture of HF, given that in some cases there is a sudden progression of the disease and significant sudden cardiac death occurrence[49,50].

HFA-ESC proposed criteria on which patients would be referred to an AHFC and they include clinical, laboratory, imaging parameters and risk assessment models shown in **Table 2**[9].

It is important to point out that more than two hospitalizations in the last 12 months indicate a very high risk of a bad outcome. Those patients have a one-year mortality rate of more than 40%. The ideal time for referring a patient to competent centres is the period in which irreversible end organ damage has not yet occurred and the clinical picture is consistent with the end stage HF or the end stage can be anticipated in the near future[47].

According to the research conducted by Herr et al, at the time of referral to a tertiary centre, 51.5% of patients had LVEF <20% and 74.5% of them were dependent on inotropic support or had a temporary MCS device. The largest number of patients were referred due to worsening failure defined by progressive symptoms, therapy intolerance and hypotension. Other causes of referral included hospitalizations, use of inotropic support and cardiogenic shock. 78.3% of patients were evaluated for heart transplantation and 76.5% for MCS implantation. However, the majority of patients were not eligible for transplantation, and the most common reasons were the patient's severe condition due to end-organ dysfunction or associated comorbidities. Psychosocial reasons were also recognized. Not a single method of advanced treatment was offered in 37.4% of patients[51].

Lund et al conducted a study on the screening of candidates for advanced treatment in patients with existing cardiac re-

TABLE 2. Suggested criteria to trigger referral to an advanced heart failure centre.[9]

Clinical	• >1 HF hospitalization in last year • NYHA class III–IV • Intolerant of optimal dose of any GDMT HF drug • Increasing diuretic requirement • SBP ≤90 mmHg • Inability to perform CPET/6MWT • CRT non-responder clinically • Cachexia, unintentional weight loss • low KCCQ score • high MLHFQ score
Laboratory	• eGFR<45 mL/min/1.73m^2 • SCr ≥ 160 µmol/L • K >5.2 or <3.5 mmol/L • Hyponatraemia • Hb ≤120 g/L • NT-proBNP ≥1000 pg/mL • Abnormal liver function test • Low albumin
Imaging	• LVEF ≤30% • Large area of akinesis/dyskinesis or aneurysm • moderate-severe mitral regurgitation • RV dysfunction • PA pressure ≥50 mmHg • Moderate-severe tricuspid regurgitation • Difficult to grade aortic stenosis • IVC dilated or without respiratory variation
Risk score data	• MAGGIC predicted survival ≤80% at 1 year • SHFM predicted survival ≤80% at 1 year

6MWT – 6-min walk test; CPET – cardiopulmonary exercise test; CRT – cardiac resynchronization therapy; eGFR – estimated glomerular filtration rate; GDMT – guideline-directed medical therapy; Hb – haemoglobin; HF – heart failure; IVC – inferior vena cava; K – potassium; KCCQ – Kansas City Cardiomyopathy Questionnaire; LVEF – left ventricular ejection fraction; MAGGIC – Meta-Analysis Global Group in Chronic Heart Failure; MLHFQ – Minnesota Living with Heart Failure Questionnaire; Na – sodium; NT-proBNP – N-terminal pro-B-type natriuretic peptide; NYHA – New York Heart Association; PA – pulmonary artery; RV – right ventricular; SBP – systolic blood pressure; SCr – serum creatinine; SHFM – Seattle Heart Failure Model

skom terapijom srca (CRT) i/ili implantibilnim kardioverter defibrilatorom (ICD) s LVEF-om ≤40 % i NYHA III. – IV. klasom te s indikacijom za napredno liječenje. Rezultati su pokazali da 26 % bolesnika nije bilo podobno za transplantaciju srca ili ugradnju LVAD-a[52].

Prema navedenome, bolesnici se nerijetko prekasno upućuju u AHFC u trenutku kada napredno liječenje više nije moguće ili je povezano s velikom vjerojatnošću nepovoljnog ishoda, pa se stoga ističe potreba za pravodobnim prepoznavanjem progresije bolesti, kao i pravovremenim upućivanjem u nadležne centre. U svrhu postizanja pravodobnog upućivanja i poboljšanja liječenja terminalnog ZS-a predložen je koncept aktivnoga probira bolesnika kojima je potrebno napredno liječenje[9].

Najčešće primjenjivani modeli procjene rizika za nehospitalizirane bolesnike s terminalnim zatajivanjem jesu HFSS i

synchronization therapy (CRT) and/or an implantable cardioverter defibrillator (ICD) with LVEF ≤40% and NYHA class III–IV and with an indication for advanced treatment. The results showed that 26% of patients were not eligible for heart transplantation or LVAD implantation[52].

According to the above, patients are often referred to an AHFC too late, at a time when advanced treatment is no longer possible or is associated with a high probability of an unfavourable outcome. Therefore, the need for timely recognition of disease progression as well as timely referral to competent centres is emphasized. In order to achieve timely referral and improve the treatment of end-stage HF, the concept of active screening of patients who need advanced treatment was proposed[9].

The most commonly used risk assessment models for non-hospitalized patients with end-stage HF are the Heart Fail-

SHFM, te se primjenjuju u evaluaciji bolesnika za transplantaciju srca. Pokazalo se da SHFM umanjuje jednogodišnji mortalitet te potrebu za hitnom transplantacijom i ugradnjom LVAD-a, pa se stoga primjenjuje u kombinaciji s kardiopulmonalnim testom opterećenja tijekom odlučivanja o uvrštavanju na transplantacijsku listu[53]. Predloženo je i nekoliko modela stratifikacije rizika za selekciju bolesnika za ugradnju MCS-a, međutim, većina modela usmjerena je na specifične uređaje i ne uzimaju u obzir druga važna stanja poput krhkosti bolesnika i psihosocijalne potpore[54].

Ako bolesnici ne toleriraju GDMT i dalje su značajno simptomatski, potrebno je kao sljedeću terapijsku opciju razmotriti transplantaciju srca i ugradnju MCS-a[9,55]. Dijagram liječenja terminalnog HFrEF-a prikazan je na **slici 3**[30].

ure Survival Score (HFSS) and the Seattle Heart Failure Model (SHFM) which are used to evaluate patients for heart transplantation. SHFM has been shown to reduce 1-year mortality and the need for urgent transplantation and LVAD implantation, so it is used in combination with cardiopulmonary exercise test while deciding on listing for transplantation[53]. Several risk stratification models have been proposed for selecting patients for MCS implantation; however, most models are focused on specific devices and do not take into account other important conditions such as patient frailty and psychosocial support[54].

If patients do not tolerate GDMT and are still significantly symptomatic, it is necessary to consider heart transplantation and MCS implantation as the next therapeutic option[9,55]. The treatment for end-stage HFrEF is shown in **Figure 3**[30].

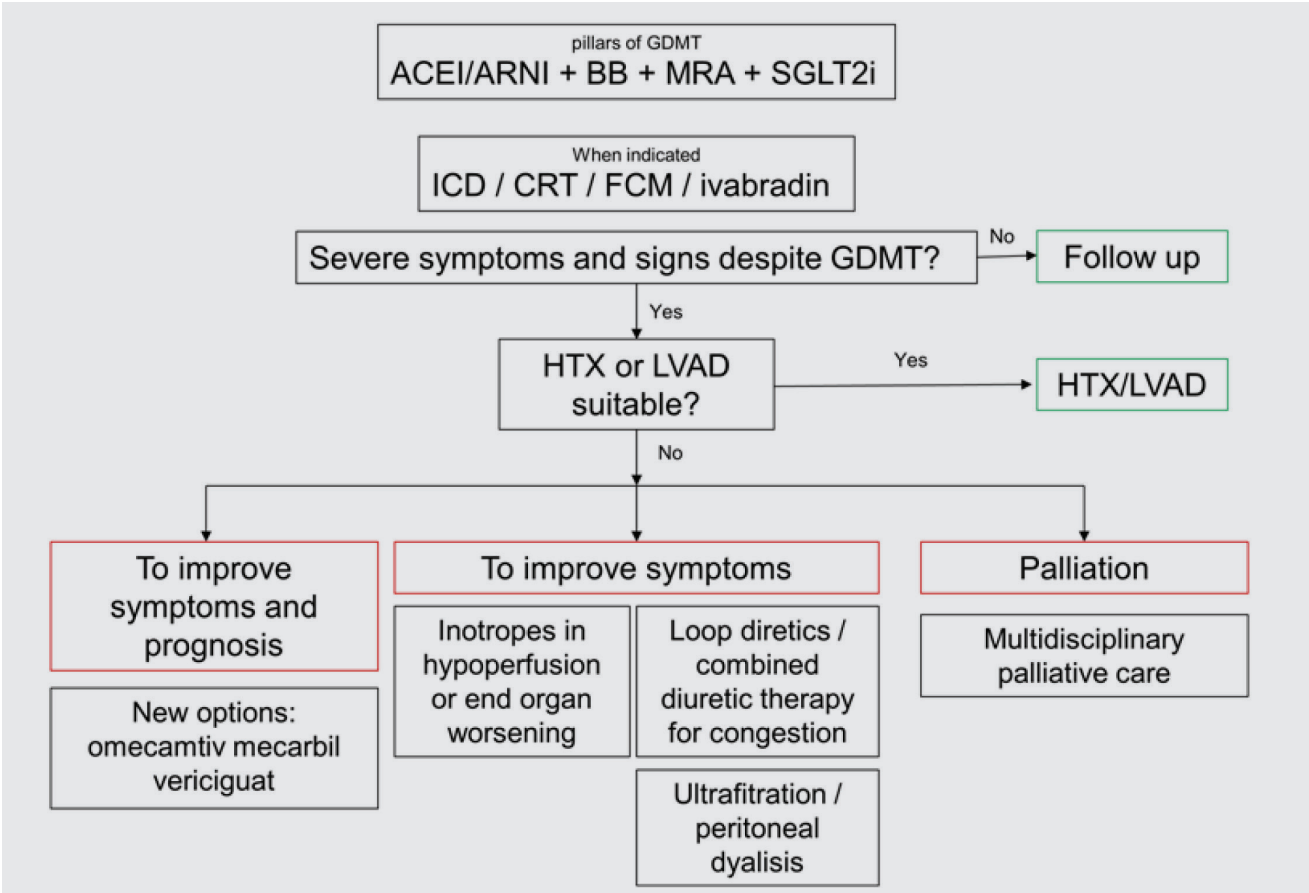

FIGURE 3. Algorithm for advanced heart failure management (adjusted from[30]).
ACEi – angiotensin-converting enzyme inhibitors; ARNI – angiotensin receptor neprilysin inhibitor; BB – beta blockers; CRT – cardiac resynchronization therapy; FCM – ferric carboxymaltose; GDMT – guideline-directed medical therapy; HFrEF – heart failure with reduced ejection fraction; HTx – heart transplantation; ICD – implantable cardioverter defibrillator; LVAD – left ventricular assist device; MRA – mineralocorticoid receptor antagonists; SGLT2 – sodium-glucose co-transporter 2

U slučaju naglog pogoršanja ili kompromitirane funkcije ciljnih organa, a, ako nije riječ o palijativnom bolesniku, primjenjuje se kratkoročna terapija koja uključuje inotropnu potporu, primjenu intravenskih vazodilatatora i vazopresora te ugradnju kratkoročnih MCS-a poput ekstrakorporalne membranske oksigenacije (ECMO)[9].

In case of a sudden deterioration or compromised function of end organs, and if it is not a palliative patient, short-term therapy is applied, which includes inotropic support, the use of intravenous vasodilators and vasopressors and the implantation of a short-term MCS device such as extracorporeal membrane oxygenation (ECMO)[9].

Transplantacija srca

Transplantacija srca zlatni je standard liječenja terminalnog ZS-a i ona znatno poboljšava kvalitetu bolesnikova života. Posttransplantacijsko jednogodišnje preživljenje iznosi oko 90 % s medijanom preživljenja od 12,5 godina[1,56]. Broj se bolesnika s terminalnim ZS-om povećava, no ograničen je broj donorskih organa, a upravo je taj nerazmjer u broju donora i primatelja glavni limitirajući čimbenik u transplantaciji srca. Nadalje, sve je veći broj kompleksnih kandidata, odnosno starijih od 65 godina, senzibiliziranih na HLA (ljudski leukocitni antigeni) i s ugrađenim MCS uređajem[57]. Kompleksniji kandidati imaju veći rizik od razvoja primarne disfunkcije presatka (PGD) i odbacivanje presatka posredovano protutijelima (AMR), što su ujedno vodeći izazovi u posttransplantacijskom razdoblju uz vaskulopatiju grafta (CAV) i kasnu disfunkciju presatka[1,57].

Jedan od preduvjeta za uspješan ishod transplantacije jest dobar odabir kandidata. Prije uvrštavanja na listu bolesnici moraju proći detaljnu obradu kako bi se potvrdila indikacija za zahvat te isključile moguće kontraindikacije. Dio kontraindikacija je relativan i potrebno ih je razmotriti u kontekstu cjelokupne kliničke slike[58,59].

Vodeći uzroci ZS-a zbog kojih se u bolesnika mora obaviti transplantacija jesu dilatacijska kardiomiopatija (51 %) i ishemijska kardiomiopatija (32 %)[56]. Jedan od najvažnijih kriterija pri postavljanju indikacije za elektivnu transplantacijsku listu funkcijski je kapacitet bolesnika, a za njegovu objektivizaciju primjenjuje se kardiopulmonalni test opterećenja i/ili 6MWT. Transplantacija srca indicirana je u bolesnika s vršnom potrošnjom kisika (VO_2) na kardiopulmonalnom testu opterećenja ≤12 mL/kg/min, odnosno ≤14 mL/kg/min ako bolesnik ne tolerira beta-blokatore. Nadalje, uvrštavanje na transplantacijsku listu indicirano je u žena i u osoba mlađih od <50 godina ako postignu vršni VO_2 ≤50 % prediktivne vrijednosti na testu opterećenjem. Ako bolesnici nisu kadri izvesti maksimalan test opterećenja, tada se kao dodatni marker može uporabiti ventilacijski ekvivalent za ugljikov dioksid (VE/VCO_2) te je indicirano uvrštavanje na listu ako je VE/VCO_2 >35[53]. Uz kardiopulmonalni test opterećenja rabe se i modeli procjene rizika, a transplantaciju treba razmotriti ako je procijenjeno jednogodišnje preživljenje prema SHFM <80 % ili ako se bolesnik prema HFSS-u nalazi u visokom ili srednjem rasponu rizika[53].

Kontraindikacije za transplantaciju srca:

- ireverzibilno povišena plućna vaskularna rezistencija ili transpulmonalni gradijent
- sistemska bolest ili druga bolest s očekivanim preživljenjem <2 godine
- aktivna infekcija
- teška periferna arterijska ili cerebrovaskularna bolest
- teška plućna bolest
- onkološka bolest (individualne procjene i stratifikacija u dogovoru s onkologom ovisno o vjerojatnosti rekurencije)
- ireverzibilno teško zatajivanje bubrega ili jetre (razmotriti blok transplantaciju)
- sistemske bolesti sa značajnim zahvaćanjem više organskih sustava
- indeks tjelesne mase >35 kg/m^2
- ovisnost o alkoholu ili drogama

Heart transplantation

Heart transplantation is the gold standard for the treatment of end-stage HF which significantly improves the patient's quality of life. Post-transplantation one-year survival is about 90% with a median survival of 12.5 years[1,56]. The number of patients with end-stage HF is increasing, but the number of donor organs is limited, and this disparity is the main limiting factor in number of heart transplantation. Furthermore, there is an increasing number of complex candidates, i.e. over 65 years of age, sensitized to human leukocyte antigens (HLA) and with an implanted MCS device[57]. More complex candidates have a higher risk of developing primary graft dysfunction (PGD) and antibody-mediated rejection (AMR), which are the main challenges in the post-transplantation period along with cardiac allograft vasculopathy (CAV) and late graft dysfunction[1,57].

One of the prerequisites for a successful transplantation outcome is a good selection of candidates. Before being enlisted for transplantation, patients must undergo a detailed examination in order to confirm the indication for the procedure and rule out possible contraindications. Some of the contraindications are relative and must be considered in the context of the overall clinical picture[58,59].

The leading causes of HF in transplant candidates are non-ischemic dilated cardiomyopathy (51%) and ischemic cardiomyopathy (32%)[56]. One of the most important criteria when setting an indication for an elective transplant list is the patient's functional capacity and the objectification is achieved with a cardiopulmonary exercise test or 6MWT. Heart transplantation is indicated in patients with peak oxygen consumption (VO2) on the cardiopulmonary exercise test ≤12 mL/kg/min, or ≤14 mL/kg/min if the patient does not tolerate beta blockers. Furthermore, inclusion on the transplant list is indicated in women and patients younger than 50 years if they achieve a peak VO2 ≤50% of the predicted value in the stress test. If patients are not able to perform the maximum load test, then the ventilation equivalent for carbon dioxide (VE/VCO2) can be used as an additional marker, and inclusion on the list is indicated if VE/VCO2 is >35[53]. In addition to the cardiopulmonary stress test, risk assessment models are also used; transplantation should be considered if the estimated one-year survival according to the SHFM is <80% or if the patient is in the high or medium risk range according to HFSS[53].

Contraindications for heart transplantation:

- irreversibly increased pulmonary vascular resistance (PVR) or transpulmonary gradient (TPG)
- systemic disease or other disease with expected survival <2 years
- active infection
- severe peripheral arterial or cerebrovascular disease
- severe lung disease
- oncological disease (individual assessments and stratification in agreement with the oncologist depending on the probability of recurrence)
- irreversible severe kidney or liver failure (consider block transplantation)
- systemic diseases with significant involvement of multiple organ systems
- body mass index > 35 kg/m^2
- alcohol or drug addiction

- nedostatak socijalne potpore koja bi osigurala adekvatnu njegu izvan bolničkog sustava[9,58].

Terminalni ZS u većini slučajeva vodi prema pogoršanju bubrežne i jetrene funkcije i karakteriziran je razvojem kardiorenalnog sindroma koji može naglo napredovati u ireverzibilni stadij. Za procjenu bubrežne funkcije rabi se klirens kreatinina i procijenjena brzina glomerularne filtracije, međutim, nije dostupan prediktivan čimbenik za procjenu oporavka bubrežne funkcije nakon transplantacije. Bubrežna disfunkcija znatno utječe na posttransplantacijski ishod, a pokatkad je potrebna kombinirana transplantacija srca i bubrega. Abnormalna funkcija jetre povezana je s lošijim ishodom nakon transplantacije, a dodatan je izazov procjena ireverzibilnog oštećenja jer slikovne metode često pružaju nedosljedne rezultate[32,53,58].

Kateterizacija desnoga srca obvezna je pretraga koja se izvodi svim kandidatima za transplantaciju srca i mora se periodično ponavljati dok bolesnik čeka na transplantacijskoj listi[53]. Potrebno je, ako je povišena, provjeriti reverzibilnost plućne vaskularne rezistencije, a u svrhu provjere primjenjuje se vazodilatacijski test primjenom vazodilatatora ili inotropne potpore. Plućna je hipertenzija reverzibilna ako je primjenom vazodilatacijskog testa plućni sistolički tlak <50 mmHg, transpulmonalni gradijent <15 mmHg i plućna vaskularna rezistencija (PVR) <4 Woodove jedinice. Bitno je naglasiti da je pad u PVR <3 Woodove jedinice uz sistolički tlak <85 mmHg na vazodilatacijskom testu povezan s većim rizikom od razvoja primarne disfunkcije grafta nakon transplantacije[31,59]. U svrhu reverzibilnosti plućne hipertenzije koja je prema testu fiksno povećana, ugrađuje se LVAD te je tom slučaju potrebno reevaluirati hemodinamske parametre. Bolesnik se može uvrstiti na transplantacijsku listu ako je kateterizacijom srca potvrđeno zadovoljavajuće poboljšanje parametara plućne vaskularne rezistencije i/ili transpulmonalnoga gradijenta[53,60,61].

Krhkost je klinički sindrom povećane vulnerabilnosti te smanjene fiziološke rezerve i funkcije koji se povezuje s postojećim komorbiditetima i starijom dobi, a posebno je izražena u bolesnika s terminalnim ZS-om. Bolesnici se smatraju krhkima ako su ispunjena tri od pet sljedećih kriterija: slaba snaga stiska, usporena brzina hodanja, nenamjeran gubitak na težini, smanjena tjelesna aktivnost i umor. Važno je naglasiti da krhkost može biti potpuno ili parcijalno reverzibilna nakon transplantacije ili ugradnje LVAD-a, što je posebno važno u selekciji bolesnika za napredno liječenje. Stoga je potrebno razlikovati krhkost povezanu s dobi s obzirom na onu povezanu sa ZS-om. Pokazalo se da je krhkost neovisni prediktor povećane smrtnosti nakon transplantacije srca i potrebno ju je procijeniti u svakog kandidata. Međutim, zbog nedostatka standardizacije otežana je njezina procjena i primjena kao definitivan kriterij za uvrštavanje na transplantacijsku listu[53,62-65].

OGRANIČEN BROJ DONORSKIH ORGANA

Prema podatcima Eurotransplanta, na kraju 2021. godine na aktivnoj listi čekanja na transplantaciju srca bilo je 1150 kandidata, a u cijeloj godini transplantacija je izvedena u 571 bolesnika. U lipnju 2022. godine na aktivnoj listi čekanja bila su 1064 bolesnika, a u vremenu od siječnja do lipnja transplantacija je obavljena u 307 bolesnika[65]. Prema *OPTN/SRTR* izvještaju, u razdoblju od 2009. do 2020. godine zabilježeno je povećanje broja kandidata uvrštenih na transplantacijsku listu od 32,5% i porast broja kandidata starijih od 65 godina.

- lack of social support that would ensure adequate care outside the hospital system[9,58].

In most cases, end-stage HF leads to deterioration of kidney and liver function and is characterized by the development of cardiorenal syndrome which can rapidly progress to an irreversible stage. Creatinine clearance and estimated glomerular filtration rate are used to assess renal function, however no predictive factor is available to assess the recovery of renal function after transplantation. Renal dysfunction significantly affects the post-transplant outcome, and sometimes a combined heart and kidney transplantation is required. Abnormal liver function is associated with a worse outcome after transplantation, and an additional challenge is the assessment of irreversible damage, given that imaging methods often provide inconsistent results[32,53,58].

Right heart catheterization is a mandatory test performed in all candidates for heart transplantation and must be repeated periodically while the patient is waiting on the transplant list[53]. If PVR or TPG are elevated, it is necessary to check its reversibility using vasodilators or inotropic support. Pulmonary hypertension is reversible if the pulmonary systolic pressure falls under 50 mmHg, transpulmonary gradient <15 mmHg and pulmonary vascular resistance (PVR) <4 Wood's units using the vasodilation test. It is important to point out that a decrease in PVR <3 Wood's units with a systolic pressure <85 mmHg on the vasodilation test is associated with a higher risk of the development of primary graft dysfunction after transplantation[31,59]. For the purpose of reversibility of pulmonary hypertension, which according to the test is absent, an LVAD is implanted, and in this case it is necessary to reevaluate the hemodynamic parameters. The patient can be included on the transplant list if an improvement in the parameters of PVR and TPG has been confirmed by heart catheterization[53,60,61].

Frailty is a clinical syndrome of increased vulnerability and reduced physiological reserve and function, which is associated with existing comorbidities and old age, and is especially pronounced in patients with end-stage HF. Patients are considered frail if three of the following five criteria are met: low grip strength, slow walking speed, unintentional weight loss, low physical activity and low energy. It is important to point out that frailty can be completely or partially reversible after transplantation or LVAD implantation, which is especially important when selecting patients for advanced treatment. Therefore, it is necessary to distinguish frailty related to age as compared to frailty related to HF. Frailty proved to be an independent predictor of increased mortality after heart transplantation and should be assessed in every candidate. However, due to the lack of standardization, its evaluation and use as a definitive criterion for inclusion on the transplant list is difficult[53,62-65].

LIMITED NUMBER OF DONOR ORGANS

According to Eurotransplant data, at the end of 2021 there were 1,150 candidates on the active heart transplant waiting list and 571 patients were transplanted in that year. In June 2022, there were 1,064 patients on the active waiting list and, in the period from January to June, 307 patients were transplanted[65]. According to the OPTN/SRTR report, in the period from 2009 to 2020 there was an increase in the number of candidates included on the transplant list by 32.5% and an increase in the number of candidates over the age of 65. Furthermore, there was also an increase in the number of can-

Nadalje, zabilježen je i porast broja kandidata s ugrađenim uređajem za potporu miokardu, pri čemu je 36,4 % kandidata imalo ugrađen uređaj u trenutku uvrštavanja na transplantacijsku listu[66].

Povećanje broja kandidata uvrštenih na transplantacijsku listu dodatno utječe na nerazmjer u broju primatelja i donora organa i, posljedično tomu, bolesnici tijekom sve duljeg razdoblja čekaju presadak[32]. Prema izvještaju Eurotransplanta, samo 42 % kandidata uvrštenih na listu primit će presadak unutar jedne godine, a 58 % nakon tri godine čekanja. Tijekom prve godine čekanja od 2014. do 2018. godine preminulo je 11 % bolesnika, a s liste je uklonjeno 2 % kandidata[67].

U nastojanju da se poveća broj dostupnih donorskih organa proširili su se kriteriji za odabir presatka i zabilježen je porast u dobi donora i primatelja organa koji je posebno izražen u Europi. Prosječna je dob primatelja presatka 55 godina, a donora 35 godina[56]. S druge strane, presadak starijeg donora može poboljšati preživljenje i kvalitetu života starijih primatelja ako su oni pomno odabrani te se na taj način može povećati broj dostupnih donora[58]. Prema nekim istraživanjima, nema značajne razlike u preživljenju među bolesnicima koji prime presadak donora starijeg od 50 godina u usporedbi s onima koji prime presadak mlađeg donora[68-70].

Prioritetni bolesnici za transplantaciju jesu oni s ugrađenim uređajima za kratkoročan MCS, ovisni o inotropnoj potpori i bolesnici s učestalim nerješivim malignim aritmijama.

Zbog svega navedenog, dulje čekanje na listi očekuje uglavnom stabilne bolesnike, osobito one na LVAD-u, a sve veći je udio i senzibiliziranih bolesnika kojima je sužen izbor donora. Prema ISHLT registru, 17,9 % bolesnika ima povišena panel reaktivna protutijela (PRA >20 %), a smatra se da je broj senzibiliziranih bolesnika u porastu zbog sve češće ugradnje MCS uređaja kao terapije premoštenja[55,71,72]. Sustav alokacije treba unaprjeđivati da bi se optimizirali resursi na pravedan i etičan način, što je posebno izazovno jer se očekuje daljnje povećanje odnosa potražnje i ponude organa[73].

Mehanička cirkulacijska potpora

Ograničen broj donorskih organa i porast broja bolesnika koji nisu kandidati za transplantaciju srca rezultirao je napretkom tehnologije u izradbi MCS uređaja i njihove primjene u liječenju bolesnika s terminalnim ZS-om. MCS se može ugraditi perkutano ili kirurški, a razlikujemo uređaje za kratkoročnu i dugoročnu primjenu. Kratkoročni se uređaji primjenjuju tijekom nekoliko dana ili tjedana u svrhu postizanja stabilizacije u kardiogenom šoku, najčešće kao terapija premoštenja do odluke (BTD) ili oporavka (BTR). Međutim, briga za bolesnike s ugrađenim kratkoročnim uređajima vrlo je kompleksna i zahtijeva donošenje odluke o uklanjanju uređaja ako ne nastupi oporavak funkcije i nema izlazne strategije. Dugoročni se uređaji primjenjuju u pomno odabranih bolesnika kao terapija premoštenja do transplantacije srca (BTT) ili kandidature (BTC), a u porastu je i broj ugrađenih uređaja kao destinacijska terapija (DT) u bolesnika koji nisu kandidati za transplantaciju (**tablica 3**)[1,54].

Evaluacija i odabir kandidata uz pravodobno razmatranje ugradnje uređaja za MCS temelj su za uspješan ishod liječenja. Kandidati za ovaj oblik liječenja uznapredovalog ZS-a bolesnici su s perzistentnim teškim simptomima unatoč optimalnoj terapiji, bez teške disfunkcije desne klijetke i/ili teške

didates with an implanted device for left ventricular support, whereby 36.4% of candidates had an implanted device at the time of inclusion on the transplant list[66].

The increase in the number of candidates included on the transplant list additionally affects the imbalance in the number of organ recipients and donors, and as a result, patients wait for a transplant for an increasingly longer period of time[32]. According to the Eurotransplant report, only 42% of candidates on the list will receive a transplant within one year, and 58% after three years of waiting. During the first year of waiting in the period from 2014 to 2018, 11% of patients died, and 2% of candidates were removed from the list[67].

In an effort to increase the number of available donor organs, the criteria for transplant selection have been expanded and there has been an increase in the age of organ donors and recipients, which is particularly noticeable in Europe. The average age of transplant recipients is 55 and donors 35[56]. On the other hand, a transplant from an elderly donor can improve the survival and quality of life of elderly recipients if they are carefully selected, thus increasing the number of available donors[58]. According to some studies, there is no significant difference in survival between patients who receive a transplant from a donor older than 50 years compared to those who receive a transplant from a younger donor[68-70].

Priority patients for transplantation are those with implanted devices for short-term MCS, those who depend on inotropic support and patients with frequent intractable malignant arrhythmias.

Due to all of the above, a longer wait on the list is expected mainly for stable patients, especially those on LVAD, and there is an increasing share of sensitized patients whose choice of donors is narrow. According to the ISHLT registry, 17.9% of patients have elevated panel reactive antibodies (PRA > 20%), and it is believed that the number of sensitized patients is increasing due to the increasingly frequent MCS implantation as bridge therapy[55,71,72]. The allocation system needs to be improved in order to optimize resources in a fair and ethical manner, which is especially challenging because a further increase in the organ demand/supply ratio is expected[73].

Mechanical circulatory support

The limited number of donor organs and the increase in the number of patients who are not eligible for heart transplantation have resulted in the advancement in MCS technology and its use in the treatment of patients with end-stage HF. MCS can be implanted percutaneously or surgically, and there are devices for short-term and long-term use. Short-term devices are used over several days or weeks in order to achieve cardiogenic shock stabilization, most often as a bridge to decision (BTD) or a bridge to recovery (BTR). Care for patients with implanted short-term devices is very complex and requires a decision to remove the device if there is no recovery of function and no exit strategy. Long-term devices are used in carefully selected patients as a bridge therapy until heart transplantation (bridge to transplantation, BTT) or a bridge to candidacy (BTC), and the number of implanted devices as destination therapy (DT) in patients who are not candidates for transplantation is increasing (**table 3**)[1,54].

Evaluation and selection of candidates along with timely MCS consideration are the foundation for a successful treatment outcome. Candidates for this type of treatment of advanced HF are patients with persistent severe symptoms despite optimal therapy, without severe right ventricular dys-

TABLE 3. Indications and reasons for mechanical circulatory support implantation (adjusted from[1]).

Bridge to decision (BTD)/ Bridge to bridge (BTB)	Short-term MCS (ECMO or Impella) in patients with cardiogenic shock until stabilization and evaluation for eligibility for long-term VAD therapy or heart transplant
Bridge to candidacy (BTC)	MCS (usually LVAD) to improve end-organ function and/or to make an ineligible patient eligible for heart transplantation
Bridge to transplantation (BTT)	Use of MCS (LVAD, BiVAD or TAH) to keep a patient alive before transplantation until a donor organ becomes available
Bridge to recovery (BTR)	Use of MCS (short-term or long-term) to keep a patient alive until cardiac function recovers sufficiently to remove MCS
Destination therapy (DT)	Long-term use of MCS (LVAD) as an alternative to transplantation in patients with end-stage HF ineligible for transplantation

BiVAD – biventricular assist device; ECMO – extracorporeal membrane oxygenation; HF – heart failure; LVAD – left ventricular assist device; MCS – mechanical circulatory support; TAH – total artificial heart; VAD – ventricular assist device

trikuspidalne regurgitacije, sa stabilnim psihosocijalnim statusom i bez kontraindikacija, i koji, usto, zadovoljavaju barem jedan od sljedećih kriterija:

- LVEF <25 % i ne podnose napor, ili ako je bolesnik kadar izvesti kardiopulmonalni test opterećenja uz vršni VO_2 <12 mL/kg/min i/ili <50 % prediktivne vrijednosti maksimalnog VO_2
- ≥3 hospitalizacije u prethodnih 12 mjeseci bez jasnoga precipitirajućeg uzroka
- ovisnost o intravenskoj inotropnoj potpori ili o kratkoročnom MCS-u
- progresivna disfunkcija ciljnih organa (pogoršanje bubrežne i/ili jetrene funkcije, plućna hipertenzija tipa 2, kardijalna kaheksija) zbog smanjene perfuzije koja nije posljedica niskoga ventrikularnog tlaka punjenja (PCWP ≥20 mmHg i sistolički krvni tlak ≤90 mmHg i srčani indeks ≤2 L/min/m^2)[1].

U selekciji bolesnika za ugradnju uređaja za MCS primjenjuje se INTERMACS klasifikacija, prema kojoj su bolesnici podijeljeni u 7 grupa na temelju kliničke slike terminalnog ZS-a:

- INTERMACS 1 – kardiogeni šok – intervencija potrebna unutar nekoliko sati
- INTERMACS 2 – progresivno pogoršanje uz eskalaciju inotropne potpore – intervencija potrebna unutar nekoliko dana
- INTERMACS 3 – bolesnik stabilan uz inotropnu potporu o kojoj je ovisan – elektivna intervencija unutar nekoliko tjedana ili mjeseci
- INTERMACS 4 – učestale dekompenzacije i tegobe u minimalnom naporu (*frequent flyer*) – elektivna intervencija unutar nekoliko tjedana ili mjeseci
- INTERMACS 5 – bez tegoba u mirovanju i osnovnoj minimalnoj aktivnosti – varijabilna urgencija intervencije
- INTERMACS 6 – *walking wounded* – bolesnik može izići iz kuće, no ubrzano se u malo jače smislenoj aktivnosti umara – varijabilna urgencija intervencije
- INTERMACS 7 – NYHA III. stupanj – bez recentnih dekompenzacija – razmotriti liječenje bez intervencije[1].

function and/or severe tricuspid regurgitation, with a stable psychosocial status and without contraindications, and who also meet at least one of the following criteria:

- LVEF <25% and unable to tolerate exercise, or if the patient is able to perform a cardiopulmonary exercise test with a peak VO_2 <12 ml/kg/min and/or <50% of the predicted maximum VO_2
- ≥3 hospitalizations in the previous 12 months without a clear precipitating cause
- dependence on intravenous inotropic support or a short-term MCS
- progressive end-organ dysfunction (deterioration of renal and/or liver function, type 2 pulmonary hypertension, cardiac cachexia) due to reduced perfusion and not to inadequately low ventricular filling pressure (PCWP ≥20 mmHg, systolic blood pressure ≤90 mmHg, cardiac index ≤2 L/min/m2)[1].

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) classification is used for selecting patients for MCS implantation. Patients are divided into 7 groups based on the clinical picture of end-stage HF:

- INTERMACS 1 – cardiogenic shock – intervention required within a few hours
- INTERMACS 2 – progressive decline with escalation of inotropic support – intervention required within days
- INTERMACS 3 – patient stable but inotrope dependent – elective intervention within a few weeks or months
- INTERMACS 4 – frequent decompensation and discomfort at minimum exertion ('frequent flyer') – elective intervention within a few weeks or months
- INTERMACS 5 – no complaints at rest and basic minimal activity – variable urgency of intervention
- INTERMACS 6 – 'walking wounded' – patient can leave the house, but has fatigue after the first few minutes of any meaningful activity – variable urgency of intervention
- INTERMACS 7 – NYHA class III – without recent decompensation – consider treatment without intervention[1].

Bolesnici koji su upućeni na ugradnju većinom su klasificirani kao profili 1 – 4, međutim, bitno je istaknuti da je profil 1 povezan s visokim mortalitetom nakon ugradnje LVAD-a[54]. U bolesnika klasificiranih kao INTERMACS profili 1 i 2 ugrađuju se kratkoročni MCS kao premoštenje do odluke ili do ugradnje dugoročnih uređaja ili hitne transplantacije[1]. Ugradnja dugotrajnog LVAD-a treba se razmotriti u bolesnika s INTERMACS profilom 2 – 4, ali i u onih profila 5 i 6 ako imaju neke od sljedećih čimbenika visokog rizika: ponavljane hospitalizacije, progresivno zatajivanje ciljnih organa, refraktorna kongestija, nemogućnost obavljanja spiroergometrije ili ostvarena vršna potrošnja kisika <12 mL/min/kg ili <50 % očekivane vrijednosti[1].

Međutim, selekcija bolesnika samo na temelju INTERMACS profila nije dovoljna i potrebno je u obzir uzeti i druge čimbenike poput funkcije ciljnih organa, dobi, spola, krhkosti i psihosocijalnoga statusa[50].

Apsolutne kontraindikacije za ugradnju uređaja jesu ireverzibilne neurološke ozljede, sistemske bolesti koje utječu na preživljenje, diseminirana maligna bolest s malom šansom za preživljenje, teške koagulopatije, postojeća kontraindikacija za primjenu antikoagulantne terapije, značajna aortalna ili periferna arterijska bolest, znatni kognitivni i/ili psihosocijalni problemi[54]. Bolesnici u kojih se razmatra ugradnja MCS-a moraju biti u mogućnosti tolerirati antikoagulantnu terapiju nužnu za prevenciju tromboze pumpe, a trenutačno se primjenjuje heparin i/ili varfarin s ciljnim INR-om u rasponu 2,0 – 3,0[54].

Manji dio bolesnika s biventrikularnom kardiomiopatijom bit će kandidati za BiVAD (uređaj za biventrikularnu potporu) ili totalno umjetno srce.

Ishodi bolesnika liječenih trajnim LVAD uređajima znatno su poboljšani tijekom posljednjih godina, osobito uz aktualnu generaciju pumpe HeartMate3 (Abbott, SAD). Prema zadnjem INTERMACS izvještaju iz 2023. godine, jednogodišnje preživljenje nakon ugradnje najnovijih LVAD-a iznosi 86 %, a petogodišnje 64 %, gotovo usporedivo kao i nakon transplantacije srca. Velika je većina bolesnika (82,3 %) LVAD dobila kao destinacijsku terapiju, što je mnogo veći udio u usporedbi s prijašnjim razdobljem (samo 44 % u 2013. godini). Manje od 3 % bolesnika koji su dobili LVAD bilo je INTERMACS profila >4. Srčani je presadak u indikaciji BTT u pet godina dobilo 54 % bolesnika, a 26 % ih je još bilo živo[74]. Istraživanje *MOMENTUM 3* bilo je do sada najveća LVAD studija koja je pokazala dvogodišnje preživljenje od gotovo 80 %, a petogodišnje preživljenje na HeartMate3 LVAD-u od gotovo 60 %[75]. Slično 5-godišnje preživljenje opisano je i u drugim publikacijama koje su analizirale velike registre bolesnika s LVAD-om[74,76].

Dobna granica za ugradnju LVAD-a nije fiksno određena te je bolesnike potrebno uvijek procjenjivati u širem aspektu. U velikoga broja bolesnika u starijoj životnoj dobi prisutni su značajni komorbiditeti koji mogu utjecati na ishod liječenja poput krhkosti i multiorganske disfunkcije[77]. Prema INTERMACS analizi, starija dob bolesnika povezana je s lošijim ishodom nakon ugradnje LVAD-a i jednogodišnje preživljenje u bolesnika ≥75 godina iznosilo je 69,6 %, a dvogodišnje 46,2 %. Također se pokazalo da je dob bolesnika važan prediktor mortaliteta nakon ugradnje LVAD-a te da stariji bolesnici imaju veću incidenciju gastrointestinalnog krvarenja[78]. Međutim, u drugom je istraživanju zabilježeno slično preživljenje u bolesnika starijih od 70 godina s ugrađenim LVAD-om u odno-

Patients referred for implantation are mostly classified as INTERMACS 1–4. However, it is important to point out that profile 1 is associated with high mortality after LVAD implantation[54]. In patients classified as INTERMACS 1 and 2, a short-term MCS is implanted as a bridge to decision or to implantation of long-term devices or to urgent transplantation[1]. Implantation of a long-term LVAD should be considered in patients of INTERMACS 2–4, but also in INTERMACS 5 and 6 if they have some of the following high-risk factors: repeated hospitalizations, progressive end organ failure, refractory congestion, inability to perform cardiopulmonary exercise test or achieved peak oxygen consumption <12 mL/min/kg or <50% of expected value[1].

However, the selection of patients based only on the INTERMACS profile is not sufficient and it is necessary to take into account other factors such as end organ function, age, gender, frailty and psychosocial status[50].

Absolute contraindications for implanting a device are irreversible neurological injuries, systemic diseases that affect survival, disseminated malignant disease with a low chance of survival, severe coagulopathies, existing contraindications for the use of anticoagulant therapy, significant aortic or peripheral arterial disease, significant cognitive and/or psychosocial problems[54]. Patients considered for MCS implantation must be able to tolerate the anticoagulant therapy necessary to prevent pump thrombosis. Currently, initially heparin and then warfarin is administered with a target INR in the range of 2.0-3.0[54].

A minority of patients with biventricular cardiomyopathy will be eligible for a biventricular assist device (BiVAD) or a total artificial heart.

Outcomes of patients treated with permanent LVAD devices have improved significantly in recent years, especially with the current generation of HeartMate3 pumps (Abbott, USA). According to the latest INTERMACS report from 2023, one-year survival after latest LVAD implantation is 86%, and five-year survival is 64%, almost comparable to that after heart transplantation. The vast majority of patients (82.3%) received LVAD as destination therapy, which is a much higher share compared to the earlier period (only 44% in 2013). Less than 3% of patients who received an LVAD had an INTERMACS profile > 4. In the BTT indication, 54% of patients received a heart transplant within five years, and 26% of them were still alive[74]. The MOMENTUM 3 study has been the largest LVAD study to date, showing a two-year survival of almost 80%, and a five-year survival on the HeartMate3 LVAD of almost 60%[75]. Similar 5-year survival was also described in other publications that analysed large registries of patients with LVAD[74,76].

The age limit for LVAD implantation is not fixed, and patients should always be evaluated in a broader aspect. A large number of elderly patients have significant comorbidities that can affect treatment outcome, such as frailty and multiorgan dysfunction[77]. According to the INTERMACS analysis, older age is associated with a worse outcome after LVAD implantation; one-year survival in patients ≥ 75 years was 69.6% and two-year survival was 46.2%. Furthermore, it was shown that age is a significant predictor of mortality after LVAD implantation and that older patients have a higher incidence of gastrointestinal bleeding[78]. However, another study reported similar survival in patients above 70 years of age with an implanted

su prema mlađima, a učestalost komplikacija također je bila slična u starijih i mlađih bolesnika[79].

Krhkost je povezana s većim mortalitetom u bolesnika s terminalnim zatajivanjem kojima je ugrađen LVAD, a ujedno i produljuje vrijeme trajanja hospitalizacije. Krhkost povećava šansu za pojavu neželjenih događaja u bolesnika s ugrađenim LVAD-om i zato je potrebno uzeti u obzir potencijalne prednosti i rizike od ugradnje u krhkih bolesnika[80]. Međutim, pokazalo se da nakon ugradnje uređaja može nastupiti regresija krhkosti. Maurer *i sur.* proveli su istraživanje koje je uključivalo krhke bolesnike starije od 60 godina koji su bili kandidati za ugradnju LVAD-a kao DT. Krhkost je procijenjena prije i nakon ugradnje, a zabilježeno je smanjenje krhkosti u prosječno 50 % bolesnika s terminalnim ZS-om nakon ugradnje LVAD-a. Također, regresija krhkosti utjecala je i na poboljšanje kvalitete života i na smanjenje broja hospitalizacija[81]. Pretpostavlja se da je razlika u ishodu nakon ugradnje uređaja i transplantacije srca u krhkih bolesnika ovisila o kardijalnim i nekardijalnim uzrocima krhkosti. Nadalje, pokazalo se da krhkost može biti potpuno ili parcijalno reverzibilna nakon ugradnje LVAD-a kao BTT u mlađih bolesnika s terminalnim ZS-om, što je potrebno uzeti u obzir tijekom evaluacije bolesnika. Potrebna su daljnja istraživanja za otkrivanje čimbenika s pomoću kojih bi se razlikovala reverzibilna i ireverzibilna krhkost[62].

Značajna aortalna regurgitacija u kandidata za ugradnju LVAD-a rezultira zatvorenim krugom u cirkulaciji između lijeve klijetke i uređaja. Stoga se zalistak u tom slučaju treba popraviti ili zamijeniti uz istodobnu ugradnju LVAD-a, a u većini slučajeva ugrađuje se bioprostetički zalistak jer su mehanički zalistci povezani s većim rizikom od tromboze. Već ugrađene mehaničke zaliske prije ugradnje uređaja preporučeno je zamijeniti bioprostetičkim[40,82].

Bubrežnu disfunkciju u bolesnika s terminalnim ZS-om potrebno je klasificirati kao primarnu ili sekundarnu jer sekundarna disfunkcija može postati reverzibilna nakon ugradnje LVAD-a. Značajna disfunkcija rizičan je čimbenik za rano zatajivanje desne klijetke, infekcije i povećan mortalitet u bolesnika s ugrađenim LVAD-om. Potrebno je isključiti primarnu ireverzibilnu bubrežnu bolest sa značajnom disfunkcijom jer se smatra kontraindikacijom za ugradnju dugoročnih MCS-a zbog loše prognoze[77,83].

Zatajivanje desne klijetke važna je komplikacija koja se pojavljuje u 25 – 30 % bolesnika nakon ugradnje LVAD-a[75]. Tijekom evaluacije i selekcije nužno je identificirati bolesnike s visokim rizikom od razvoj zatajivanja desne klijetke jer je povezana s visokim postoperativnim mortalitetom i morbiditetom. Prediktori zatajivanja desne klijetke uključuju indeks rada desne klijetke <250 mmHg x mL/m^2, omjer centralnoga venskog tlaka i plućnoga kapilarnog tlaka (CVP/PCWP) >0,63, PAPi (indeks pulsatilnosti plućne arterije) <2,0 te ehokardiografski dokazanu disfunkciju desne klijetke[54,84]. Unatoč tomu, nisu poznate točne mjere funkcije desne klijetke koje bi značile apsolutnu kontraindikaciju za ugradnju LVAD-a.

Kandidati za ugradnju LVAD-a moraju biti visokomotivirani i suradljivi u cjelokupnome procesu liječenja. Konzumacija alkohola i droga kontraindikacija su za ugradnju LVAD-a. Iznimno je važna podrška obitelji i okruženja u prilagodbi bolesnika na nov način života, a nedostatak potpore smatra se kontraindikacijom za ugradnju. Potrebno je psihosocijalnom evaluacijom utvrditi stabilnost i dostupnost obiteljske podrške koja je potrebna radi psihološke potpore, pomoći oko

LVAD compared to younger patients, and the frequency of complications was also similar between the groups[79].

Frailty is associated with higher mortality in patients with end-stage HF and LVAD implantation, and also prolongs the duration of hospitalization. Frailty increases the chance of adverse events in patients with an implanted LVAD, and therefore it is necessary to take into account the potential benefits and risks of implantation in frail patients[80]. However, regression of frailty may occur after device implantation. Maurer et al conducted a study involving frail patients above 60 years of age who were eligible for LVAD implantation as DT. Frailty was assessed before and after implantation, and a decrease in frailty was noted in an average of 50% of patients. Also, frailty regression had an effect on improving the quality of life and reducing the number of hospitalizations[81]. It is assumed that the difference in outcome after device implantation and heart transplantation in frail patients depends on cardiac and non-cardiac causes of frailty. Furthermore, frailty can be fully or partially reversible after LVAD implantation as a BTT in younger patients with end-stage HF, which should be taken into account during patient evaluation. Further research is needed to uncover factors to differentiate between reversible and irreversible frailty[62].

Significant aortic regurgitation in LVAD candidates results in a closed circuit in the circulation between the left ventricle and the device. Therefore, in that scenario the valve should be repaired or replaced when implanting an LVAD. In most cases, a bioprosthetic valve is implanted, considering that mechanical valves are associated with a higher risk of thrombosis. It is recommended to replace the already implanted mechanical valves with bioprosthetic valves before device implantation[40,82].

Renal dysfunction in patients with end-stage HF should be classified as primary or secondary, given that secondary dysfunction may become reversible after LVAD implantation. Significant dysfunction is a risk factor for early right ventricular failure, infection and increased mortality in patients with an implanted LVAD. It is necessary to rule out primary irreversible kidney disease with significant dysfunction, as it is considered a contraindication for long-term MCS implantation due to the poor prognosis[77,83].

Right ventricular failure is a significant complication that occurs in 25–30% of patients after LVAD implantation[75]. During evaluation and selection, it is necessary to identify patients with a high risk of developing right ventricular failure, given that it is associated with high postoperative mortality and morbidity. Predictors of right ventricular failure include right ventricular function index <250 mmHgxmL/m^2, central venous pressure to pulmonary capillary wedge pressure (CVP/PCWP) ratio >0.63, pulmonary artery pulsatility index (PAPi) <2, 0 and echocardiographically proven right ventricular dysfunction[54,84]. Nevertheless, there are no known exact levels of right ventricular function that would constitute an absolute contraindication for LVAD implantation.

Candidates for LVAD implantation must be highly motivated and cooperative throughout the entire treatment process. Alcohol and drug use are contraindications for LVAD implantation. The support of family and friends is extremely important in adapting the patient to a new lifestyle, and the lack of support is considered a contraindication for implantation. Psychosocial evaluation should determine the stability and

previjanja mjesta izlaza provodnika kroz kožu na abdomenu, mijenjanja baterija i nadzora uzimanja terapije. Takva je podrška nužna u bolesnika koji nisu kadri brinuti se sami o sebi, što je potrebno uzeti u obzir tijekom evaluacije[77,85,86].

Trajno ugrađeni uređaji povezani su s određenim rizicima i komplikacijama poput infekcija, krvarenja, tromboze i zatajivanja desne klijetke[40]. Prema *INTERMACS* izvještaju, nakon ugradnje uređaja najčešći uzroci rehospitalizacije uključuju krvarenje, infekcije, neurološke poremećaje i zatajivanje desne klijetke[74].

Infekcije izlazišta provodnika kroz kožu na abdomenu jedne su od najčešćih komplikacija. Većina je infekcija površinska, međutim, one se mogu proširiti u kanal na abdominalnoj stijenci prema cijelom sustavu. Kako bi se smanjio rizik od tromboze, obvezna je primjena antikoagulantne terapije. Krvarenje je vodeća komplikacija nakon ugradnje uređaja. Gastrointestinalno krvarenje smatra se vrlo izazovnom kliničkom dilemom koja utječe na liječenje bolesnika s ugrađenim LVAD-om. Najčešće nastaje u gornjem dijelu probavnog sustava, međutim, u 30 – 50 % slučajeva ne može se otkriti aktivno mjesto krvarenja, a poznato je i da LVAD može potaknuti i razvoj angiodisplazija[9,77,83,87]. Tromboza pumpe može nastati u bilo kojem dijelu LVAD-a u kojem prolazi krv te, posljedično, može rezultirati razvojem cerebrovaskularnog inzulta, disfunkcije pumpe, a u nekim slučajevima i prestankom rada pumpe, razvojem kardiogenog šoka i smrti. Zlatni standard u liječenju je zamjena pumpe, međutim, povezana je sa znatnim morbiditetom i mortalitetom. Moždani udar kao komplikacija ugradnje LVAD-a vodeći je uzrok invalidnosti i smrti u bolesnika nakon ugradnje, a rizični čimbenici za nastanak uključuju infekcije, trombozu pumpe i neadekvatnu primjenu antitrombotske terapije[88].

Palijativna skrb

Palijativna je skrb interdisciplinarni pristup usmjeren prema poboljšanju kvalitete života bolesnika i njihovih skrbnika tako da pruža tjelesnu, emocionalnu, psihosocijalnu i duhovnu potporu bolesnicima koji nisu za aktivni oblik liječenja. Iako se najčešće povezuje s bolesnicima koji boluju od malignih bolesti, vrlo je važna i u bolesnika sa ZS-om[89]. Ovakav oblik liječenja ne bi trebao nužno biti povezan s tercijarnim centrom.

Idealno vrijeme za uvođenje PC-a u ZS-u nije potpuno definirano. Razgovor o uvođenju PC-a trebalo bi svakako inicirati u bolesnika koji nisu za napredne metode liječenja, a imaju učestale rehospitalizacije vezane uz pogoršanje zatajivanja, s rekurentim šokovima ICD-a te s teškom anksioznošću i depresijom koje znatno utječu na kvalitetu života[90]. Svrha PC-a jest kontrola simptoma, smanjenje distresa, neubrzavanje ni odgađanje smrti te osiguranje potpore i pomoći da bolesnici žive što aktivnije i kvalitetnije do smrti. Adekvatno provođenje PC-a uključuje interdisciplinarnu suradnju i koordinaciju različitih sustava (medicinski, socijalni, vjerski i drugi) i specijalnosti (obiteljski liječnik, sestra, psiholog i drugi).

Prednosti uvođenja PC-a pokazale su se u istraživanju *PAL-HF* u koje je bilo uključeno 150 bolesnika s terminalnim ZS-om. Bolesnici su randomizirani u dvije grupe, od kojih je jedna imala uobičajenu skrb, a u drugoj je, uz uobičajenu, uvedena i PC. Istraživanje je pokazalo da je interdisciplinarna PC u bo-

availability of family support, which is needed for psychological support, help with dressing the driveline on the abdomen surface, changing batteries and supervising the medication. Such support is necessary for patients who are unable to take care of themselves[77,85,86].

Permanently implanted devices are associated with certain risks and complications such as infections, bleeding, thrombosis and right ventricular failure[40]. According to the INTERMACS report, the most common causes of rehospitalization after device implantation include bleeding, infections, neurological disorders and right ventricular failure[74].

Infections of the driveline on the abdomen surface are one of the most common complications. Most infections are superficial, however, they can spread through the channel on the abdominal wall to the entire system. In order to reduce the risk of thrombosis, the use of anticoagulation therapy is mandatory. Bleeding is the main complication after device implantation. Gastrointestinal bleeding is considered a very challenging clinical dilemma affecting the management of LVAD patients. It most often occurs in the upper part of the digestive system, however, in 30–50% of cases the active site of bleeding cannot be detected. It is also known that LVAD can stimulate the development of angiodysplasia[9,77,83,87]. Pump thrombosis can occur in any part of the LVAD through which blood passes. It can consequently result in the development of cerebrovascular insult, pump dysfunction and, in some cases, pump failure, the development of cardiogenic shock and death. The gold standard in treatment is pump replacement; however, it is associated with significant morbidity and mortality. Stroke as a complication of LVAD implantation is the leading cause of disability and death in patients after implantation, and risk factors for its occurrence include infections, pump thrombosis and inadequate use of antithrombotic therapy[88].

Palliative care

Palliative care is an interdisciplinary approach aimed at improving the quality of life of patients and their caregivers in a way that provides physical, emotional, psychosocial and spiritual support to patients who are not eligible for active treatment. Although it is most often associated with patients suffering from malignant diseases, it is also very important in HF patients[89]. This type of treatment should not necessarily be associated and given by a tertiary centre.

The ideal time for introducing PC in cases of HF is not fully defined. The conversation about the introduction of PC should certainly be initiated in patients who are not eligible for advanced treatment methods, and who have frequent rehospitalizations related to the worsening of their condition, with recurrent ICD shocks and with severe anxiety and depression that significantly affect the quality of life[90]. The aim of PC is to control symptoms, reduce distress, not hasten or delay death, provide support and help for patients to live as actively and as good as possible until death. Adequate implementation of PC includes interdisciplinary cooperation and coordination of different systems (medical, social, religious and others) and specialities (family doctor, nurse, psychologist and others).

The benefits of introducing PC were demonstrated in the PAL-HF study, which included 150 patients with end-stage HF. The patients were randomized into two groups, one of which

lesnika s terminalnim ZS-om rezultirala boljom kvalitetom života, smanjenjem anksioznosti i depresije[91].

U istraživanju koje su proveli Sahlollbey *i sur.* pokazalo se da je uvođenje PC-a u bolesnika s terminalnim zatajivanjem povezana sa smanjenjem broja hospitalizacija i težine simptoma te s poboljšanjem kvalitete života, ali, unatoč tomu, njezino uvođenje nije imalo utjecaja na mortalitet u usporedbi s uobičajenom skrbi[92].

Usprkos napretku u tom području, potrebno je uvesti dodatne napore za pravodobno uvođenje PC-a jer je samo 34 % bolesnika upućeno na PC u posljednjem mjesecu njihova života, a prosječno vrijeme od upućivanja do smrti iznosi manje od 2 tjedna[50].

Zaključak

Uznapredovali ZS karakteriziran je lošom prognozom unatoč napretcima u liječenju i značajan je klinički izazov. Pravodobno i smisleno upućivanje bolesnika sa ZS-om u specijalizirane centre koji se bave naprednim metodama liječenja (transplantacijom srca i ugradnjom MCS-a) iznimno je važno kako bi se poboljšala prognoza ovakvih bolesnika. Daljni napori u poboljšanju prevencije, ranog otkrivanja i liječenja ZS-a i dobra racionalizacija ograničenih resursa u liječenju uznapredovalog ZS-a nužni su kako bi se smanjila smrtnost i poboljšao život mnogih bolesnika koji boluju od ovoga kliničkog sindroma „malignog" tijeka.

received the usual care, and the other received PC in addition to the usual care. The research showed that interdisciplinary PC in patients with end-stage HF resulted in a better quality of life, reduction of anxiety and depression[91].

In a study conducted by Sahlolbey et al, it was shown that the introduction of PC in patients with end-stage HF is associated with a reduction in the number of hospitalizations, symptoms severity and quality of life improvement, but even so, its introduction had no effect on mortality compared to the usual care[92].

Despite the progress in this area, additional efforts should be made for the timely introduction of PC considering that only 34% of patients are referred to PC in the last month of their life, and the average time from referral to death is less than 2 weeks[50].

Conclusion

Advanced HF is characterized by a poor prognosis despite advances in treatment and represents a significant clinical challenge. Timely referral of HF patients to specialized centres for advanced treatment methods (heart transplantation and MCS) is extremely important in order to improve the prognosis for these patients. Further efforts to improve the prevention, early detection and treatment of HF and good allocation of limited resources in the treatment of advanced HF are necessary to reduce mortality and improve the lives of many patients suffering from this clinical syndrome with a 'malignant' course.

LITERATURE

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 Sep 21;42(36):3599-726. https://doi.org/10.1093/eurheartj/ehab368
2. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. Eur J Heart Fail. 2020 Aug;22(8):1342-56. https://doi.org/10.1002/ejhf.1858
3. Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev. 2017 Apr;3(1):7-11. https://doi.org/10.15420/cfr.2016:25:2
4. Dharmarajan K, Rich MW. Epidemiology, Pathophysiology, and Prognosis of Heart Failure in Older Adults. Heart Fail Clin. 2017 Jul;13(3):417-26. https://doi.org/10.1016/j.hfc.2017.02.001
5. van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. Eur J Heart Fail. 2016 Mar;18(3):242-52. https://doi.org/10.1002/ejhf.483
6. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail. 2019 Nov;21(11):1306-25. https://doi.org/10.1002/ejhf.1594
7. Metra M, Teerlink JR. Heart failure. The Lancet. 2017 Oct;390(10106):1981-95. https://doi.org/10.1016/S0140-6736(17)31071-1
8. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics–2016 Update: A Report From the American Heart Association. Circulation. 2016 Jan 26;133(4):e38-360. https://doi.org/10.1161/CIR.0000000000000350
9. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, et al. Advanced heart failure: a position statement of the Heart Failure Association of the European Society of Cardiology: Advanced heart failure: HFA position statement. Eur J Heart Fail. 2018 Nov;20(11):1505-35. https://doi.org/10.1002/ejhf.1236
10. Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Heart Fail. 2021 Mar 1:S1071-9164(21)00050-6. https://doi.org/10.1016/j.cardfail.2021.01.022
11. Dunlay SM, Roger VL, Killian JM, Weston SA, Schulte PJ, Subramaniam AV, et al. Advanced Heart Failure Epidemiology and Outcomes: A Population-Based Study. JACC Heart Fail. 2021 Oct;9(10):722-32. https://doi.org/10.1016/j.jchf.2021.05.009
12. Kalogeropoulos AP, Samman-Tahhan A, Hedley JS, McCue AA, Bjork JB, Markham DW, et al. Progression to Stage D Heart Failure Among Outpatients With Stage C Heart Failure and Reduced Ejection Fraction. JACC Heart Fail. 2017 Jul;5(7):528-37. https://doi.org/10.1016/j.jchf.2017.02.020
13. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 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 of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016 Aug;18(8):891-975. https://doi.org/10.1002/ejhf.592
14. Zaputović L, Zaninović Jurjević T, Ružić A. Klinička slika zatajivanja srca. Medix. 2014;20(112):90-4. Available from: https://urn.nsk.hr/urn:nbn:hr:184:920477
15. MSD priručnik dijagnostike i terapije. Placebo d.o.o Split. [Internet] 2014. [cited 2022 June 26]. Available from: http://www.msd-prirucnici.placebo.hr/msdprirucnik/kardiologija/zatajivanje-srca-i-kardiomiopatije/zatajivanje-srca
16. Masarone D, Kittleson M, Petraio A, Pacileo G. Advanced heart failure: state of the art and future directions. Rev Cardiovasc Med. 2022 Feb 8;23(2):048. https://doi.org/10.31083/j.rcm2302048
17. Colucci W, Dunlay S. Clinical manifestations and diagnosis of advanced heart failure. UpToDate. [Internet]. 2022 [cited 2022 August 23]. Available from: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-advanced-heart-failure

18. Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet. 2022 Dec 3;400(10367):1938-52. https://doi.org/10.1016/S0140-6736(22)02076-1
19. McMurray JJV, Packer M. How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction?: A Redefinition of Evidence-Based Medicine. Circulation. 2021 Mar 2;143(9):875-7. https://doi.org/10.1161/CIRCULATIONAHA.120.052926
20. Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. Eur J Heart Fail. 2021 Jun;23(6):882-894. https://doi.org/10.1002/ejhf.2149
21. Packer M, Fowler MB, Roecker EB, Coats AJS, Katus HA, Krum H, et al. Effect of Carvedilol on the Morbidity of Patients With Severe Chronic Heart Failure: Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. Circulation. 2002 Oct 22;106(17):2194-9. https://doi.org/10.1161/01.CIR.0000035653.72855.BF
22. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure. N Engl J Med. 2014 Sep 11;371(11):993-1004. https://doi.org/10.1056/NEJMoa1409077
23. Mann DL, Givertz MM, Vader JM, Starling RC, Shah P, McNulty SE, et al. Effect of Treatment With Sacubitril/Valsartan in Patients With Advanced Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial. JAMA Cardiol. 2022 Jan 1;7(1):17. https://doi.org/10.1001/jamacardio.2021.4567
24. Vader JM, Givertz MM, Starling RC, McNulty SE, Anstrom KJ, Desvigne-Nickens P, et al. Tolerability of Sacubitril/Valsartan in Patients With Advanced Heart Failure. JACC Heart Fail. 2022 Jul;10(7):449-56. https://doi.org/10.1016/j.jchf.2022.04.013
25. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure. N Engl J Med. 1999 Sep 2;341(10):709-17. https://doi.org/10.1056/NEJM199909023411001
26. Packer M, Anker SD, Butler J, Filippatos G, Ferreira JP, Pocock SJ, et al. Effect of Empagliflozin on the Clinical Stability of Patients With Heart Failure and a Reduced Ejection Fraction: The EMPEROR-Reduced Trial. Circulation. 2021 Jan 26;143(4):326-36. https://doi.org/10.1161/CIRCULATIONAHA.120.051783
27. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008. https://doi.org/10.1056/NEJMoa1911303
28. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-61. https://doi.org/10.1056/NEJMoa2107038
29. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, et al; DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22;387(12):1089-98. https://doi.org/10.1056/NEJMoa2206286
30. Tomasoni D, Vishram-Nielsen JKK, Pagnesi M, Adamo M, Lombardi CM, Gustafsson F, et al. Advanced heart failure: guideline-directed medical therapy, diuretics, inotropes, and palliative care. ESC Heart Fail. 2022 Jun;9(3):1507-23. https://doi.org/10.1002/ehf2.13859
31. Vishram-Nielsen JKK, Tomasoni D, Gustafsson F, Metra M. Contemporary Drug Treatment of Advanced Heart Failure with Reduced Ejection Fraction. Drugs. 2022 Mar;82(4):375-405. https://doi.org/10.1007/s40265-021-01666-z
32. Westerdahl DE, Kobashigawa JA. Heart Transplantation for Advanced Heart Failure. Cardiac Intensive Care. 2019 : 504-524.e2. https://doi.org/10.1016/B978-0-323-52993-8.00048-5
33. Kalmanovich E, Audurier Y, Akodad M, Mourad M, Battistella P, Agullo A, et al. Management of advanced heart failure: a review. Expert Rev Cardiovasc Ther. 2018 Nov 2;16(11):775-94. https://doi.org/10.1080/14779072.2018.1530112
34. Filippatos G, Farmakis D, Colet JC, Dickstein K, Luscher TF, Willenheimer R, et al. Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial. Eur J Heart Fail. 2013 Nov;15(11):1267-76. https://doi.org/10.1093/eurjhf/hft099
35. Armstrong PW, Pieske B, Anstrom KJ, Ezekowitz J, Hernandez AF, Butler J, et al. Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020 May 14;382(20):1883-93. https://doi.org/10.1056/NEJMoa1915928
36. Ezekowitz JA, O'Connor CM, Troughton RW, Alemayehu WG, Westerhout CM, Voors AA, et al. N-Terminal Pro-B-Type Natriuretic Peptide and Clinical Outcomes. JACC Heart Fail. 2020 Nov;8(11):931-9. https://doi.org/10.1016/j.jchf.2020.08.008
37. Farmakis D, Agostoni P, Baholli L, Bautin A, Comin-Colet J, Crespo-Leiro MG, et al. A pragmatic approach to the use of inotropes for the management of acute and advanced heart failure: An expert panel consensus. Int J Cardiol. 2019 Dec;297:83-90. https://doi.org/10.1016/j.ijcard.2019.09.005
38. Nizamic T, Murad MH, Allen LA, McIlvennan CK, Wordingham SE, Matlock DD, et al. Ambulatory Inotrope Infusions in Advanced Heart Failure. JACC Heart Fail. 2018 Sep;6(9):757-67. https://doi.org/10.1016/j.jchf.2018.03.019
39. Kini V, Kirkpatrick JN. Ethical challenges in advanced heart failure. Curr Opin Support Palliat Care. 2013 Mar;7(1):21-8. https://doi.org/10.1097/SPC.0b013e32835c4915
40. Allen LA, Stevenson LW, Grady KL, Goldstein NE, Matlock DD, Arnold RM, et al. Decision Making in Advanced Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2012 Apr 17;125(15):1928-52. https://doi.org/10.1161/CIR.0b013e31824f2173
41. O'Connor CM, Gattis WA, Uretsky BF, Adams KF, McNulty SE, Grossman SH, et al. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: Insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J. 1999 Jul;138(1 Pt 1):78-86. https://doi.org/10.1016/S0002-8703(99)70250-4
42. Cuffe MS. Short-term Intravenous Milrinone for Acute Exacerbation of Chronic Heart FailureA Randomized Controlled Trial. JAMA. 2002 Mar 27;287(12):1541. https://doi.org/10.1001/jama.287.12.1541
43. Nieminen MS, Cleland JGF, Eha J, Belenkov Y, Kivikko M, Põder P, et al. Oral levosimendan in patients with severe chronic heart failure-The PERSIST study. Eur J Heart Fail. 2008 Dec;10(12):1246-54. https://doi.org/10.1016/j.ejheart.2008.09.006
44. Altenberger J, Parissis JT, Costard-Jaeckle A, Winter A, Ebner C, Karavidas A, et al. Efficacy and safety of the pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep) study: a multicentre randomized trial. Eur J Heart Fail. 2014 Aug;16(8):898-906. https://doi.org/10.1002/ejhf.118
45. Comín-Colet J, Manito N, Segovia-Cubero J, Delgado J, García Pinilla JM, Almenar L, et al. Efficacy and safety of intermittent intravenous outpatient administration of levosimendan in patients with advanced heart failure: the LION-HEART multicentre randomised trial: Levosimendan in advanced HF: the LION-HEART trial. Eur J Heart Fail. 2018 Jul;20(7):1128-36. https://doi.org/10.1002/ejhf.1145
46. Masarone D, Melillo E, Gravino R, Errigo V, Martucci ML, Caiazzo A, et al. Inotropes in Patients with Advanced Heart Failure. Heart Fail Clin. 2021 Oct;17(4):587-98. https://doi.org/10.1016/j.hfc.2021.05.004
47. Morris AA, Khazanie P, Drazner MH, Albert NM, Breathett K, Cooper LB, et al. Guidance for Timely and Appropriate Referral of Patients With Advanced Heart Failure: A Scientific Statement From the American Heart Association. Circulation 2021 Oct 12;144(15):e238-e250. https://doi.org/10.1161/CIR.0000000000001016
48. Baumwol J. "I Need Help"–A mnemonic to aid timely referral in advanced heart failure. J Heart Lung Transplant. 2017 May;36(5):593-4. https://doi.org/10.1016/j.healun.2017.02.010
49. Thorvaldsen T, Lund LH. Focusing on Referral Rather than Selection for Advanced Heart Failure Therapies. Card Fail Rev. 2019 Feb;5(1):24-6. https://doi.org/10.15420/cfr.2018.35.1
50. Truby LK, Rogers JG. Advanced Heart Failure: Epidemiology, Diagnosis, and Therapeutic Approaches. JACC Heart Fail. 2020 Jul;8(7):523-36. https://doi.org/10.1016/j.jchf.2020.01.014
51. Herr JJ, Ravichandran A, Sheikh FH, Lala A, Chien CV, Hsiao S, et al. Practices of Referring Patients to Advanced Heart Failure Centers. J Card Fail. 2021 Nov;27(11):1251-1259. https://doi.org/10.1016/j.cardfail.2021.05.024
52. Lund LH, Trochu JN, Meyns B, Caliskan K, Shaw S, Schmitto JD, et al. Screening for heart transplantation and left ventricular assist system: results from the ScrEEning for advanced Heart Failure treatment (SEE-HF) study. Eur J Heart Fail. 2018 Jan;20(1):152-160. https://doi.org/10.1002/ejhf.975

53. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. J Heart Lung Transplant. 2016 Jan;35(1):1-23. https://doi.org/10.1016/j.healun.2015.10.023
54. Vieira JL, Ventura HO, Mehra MR. Mechanical circulatory support devices in advanced heart failure: 2020 and beyond. Prog Cardiovasc Dis. 2020 Sep-Oct;63(5):630-639. https://doi.org/10.1016/j.pcad.2020.09.003
55. Guglin M, Zucker MJ, Borlaug BA, Breen E, Cleveland J, Johnson MR, et al. Evaluation for Heart Transplantation and LVAD Implantation. J Am Coll Cardiol. 2020 Mar;75(12):1471-87. https://doi.org/10.1016/j.jacc.2020.01.034
56. Khush KK, Cherikh WS, Chambers DC, Harhay MO, Hayes D, Hsich E, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report – 2019; focus theme: Donor and recipient size match. J Heart Lung Transplant. 2019 Oct;38(10):1056-66. https://doi.org/10.1016/j.healun.2019.08.004
57. Kittleson MM, Kobashigawa JA. Cardiac Transplantation. JACC Heart Fail. 2017 Dec;5(12):857-68. https://doi.org/10.1016/j.jchf.2017.08.021
58. Bhagra SK, Pettit S, Parameshwar J. Cardiac transplantation: indications, eligibility and current outcomes. Heart. 2019 Feb;105(3):252-60. https://doi.org/10.1136/heartjnl-2018-313103
59. Samardžić J, Lovrić D, Miličić D. Transplantacija srca - indikacije, kontraindikacije i dugoročno praćenje transplantiranih bolesnika. Medix 2011;92:160-4. Available from: https://www.kardio.hr/wp-content/uploads/2011/09/Medix%2092-93_160-164.pdf
60. López-Cardoza U, Díez-López C, González-Costello J. Heart Transplant: Current Indications and Patient Selection. In: Loforte A, Montalto A, Amarelli C, editors. Heart Transplantation [Internet]. InTech; 2018 [cited 2022 July 18]. Available from: http://www.intechopen.com/books/heart-transplantation/heart-transplant-current-indications-and-patient-selection
61. Mikus E, Stepanenko A, Krabatsch T, Loforte A, Dandel M, Lehmkuhl HB, et al. Reversibility of fixed pulmonary hypertension in left ventricular assist device support recipients.Eur J Cardiothorac Surg.2011 Oct;40(4):971-7. https://doi.org/10.1016/j.ejcts.2011.01.019
62. Jha SR, Hannu MK, Chang S, Montgomery E, Harkess M, Wilhelm K, et al. The Prevalence and Prognostic Significance of Frailty in Patients With Advanced Heart Failure Referred for Heart Transplantation. Transplantation. 2016 Feb;100(2):429-36. https://doi.org/10.1097/TP.0000000000000991
63. Macdonald PS, Gorrie N, Brennan X, Aili SR, De Silva R, Jha SR, et al. The impact of frailty on mortality after heart transplantation. J Heart Lung Transplant. 2021 Feb;40(2):87-94. https://doi.org/10.1016/j.healun.2020.11.007
64. Joyce E. Frailty in Advanced Heart Failure. Heart Fail Clin. 2016 Jul;12(3):363-74. https://doi.org/10.1016/j.hfc.2016.03.006
65. Statistics-Eurotransplant.[Internet]. [cited 2022 July 18]. Available from: https://statistics.eurotransplant.org/
66. Colvin M, Smith JM, Ahn Y, Skeans MA, Messick E, Bradbrook K, et al. OPTN/SRTR 2020 Annual Data Report: Heart. Am J Transplant. 2022 March;22 Suppl 2:350-437. https://doi.org/10.1111/ajt.16977
67. Eurotransplant Annual Report. [Internet]. 2021 [cited 2022 July 19]. Available from: https://www.eurotransplant.org/wp-content/uploads/2022/06/Annual-Report-2021_LR.pdf
68. Esmailian FA, Emerson D, Megna D, Ramzy D, Levine R, Aguilar J, et al. Heart Transplantation with Older Donors: Should There Be an Age Cutoff. J Heart Lung Transplant. 2020 Apr;39(4):S43. https://doi.org/10.1016/j.healun.2020.01.1209
69. Prieto D, Correia P, Baptista M, Antunes MJ. Outcome after heart transplantation from older donor age: expanding the donor pool. Eur J Cardiothorac Surg. 2015 Apr;47(4):672-8. https://doi.org/10.1093/ejcts/ezu257
70. Singh SSA, Dalzell JR, Berry C, Al-Attar N. Primary graft dysfunction after heart transplantation: a thorn amongst the roses. Heart Fail Rev. 2019 Sep;24(5):805-20. https://doi.org/10.1007/s10741-019-09794-1
71. Khush KK, Hsich E, Potena L, Cherikh WS, Chambers DC, Harhay MO, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult heart transplantation report – 2021; Focus on recipient characteristics. J Heart Lung Transplant. 2021 Oct;40(10):1035-49. https://doi.org/10.1016/j.healun.2021.07.015
72. Patel JK. Prioritization for sensitization in heart transplantation–An approach toward greater equity. J Heart Lung Transplant. 2017 May;36(5):486-7. https://doi.org/10.1016/j.healun.2017.02.009
73. Smits JM, Samuel U, Laufer G. Bridging the gap in heart transplantation: Curr Opin Organ Transplant. 2017 Jun;22(3):221-4. https://doi.org/10.1097/MOT.0000000000000408
74. Jorde UP, Saeed O, Koehl D, Morris AA, Wood KL, Meyer DM, et al. The Society of Thoracic Surgeons Intermacs 2023 Annual Report: Focus on Magnetically Levitated Devices. Ann Thorac Surg. 2024 Jan;117(1):33-44. https://doi.org/10.1016/j.athoracsur.2023.11.004
75. Mehra MR, Goldstein DJ, Cleveland JC, Cowger JA, Hall S, Salerno CT, et al. Five-Year Outcomes in Patients With Fully Magnetically Levitated vs Axial-Flow Left Ventricular Assist Devices in the MOMENTUM 3 Randomized Trial. JAMA. 2022;328(12):1233-1242. https://doi.org/10.1001/jama.2022.16197
76. Schmitto JD, Shaw S, Garbade J, Gustafsson F, Morshuis M, Zimpfer D, et al. Fully magnetically centrifugal left ventricular assist device and long-term outcomes: the ELEVATE registry. Eur Heart J. 2024 Feb 21;45(8):613-625. https://doi.org/10.1093/eurheartj/ehad658
77. Gustafsson F, Rogers JG. Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes: LVAD therapy in HF. Eur J Heart Fail. 2017 May;19(5):595-602. https://doi.org/10.1002/ejhf.779
78. Caraballo C, DeFilippis EM, Nakagawa S, Ravindra NG, Miller PE, Mezzacappa C, et al. Clinical Outcomes After Left Ventricular Assist Device Implantation in Older Adults. JACC Heart Fail. 2019 Dec;7(12):1069-78. https://doi.org/10.1016/j.jchf.2019.10.004
79. Galand V, Flécher E, Chabanne C, Lelong B, Goéminne C, Vincentelli A, et al. Septuagenarian population has similar survival and outcomes to younger patients after left ventricular assist device implantation. Arch Cardiovasc Dis. 2020 Nov;113(11):701-9. https://doi.org/10.1016/j.acvd.2020.05.018
80. Tse G, Gong M, Wong SH, Wu WKK, Bazoukis G, Lampropoulos K, et al. Frailty and Clinical Outcomes in Advanced Heart Failure Patients Undergoing Left Ventricular Assist Device Implantation: A Systematic Review and Meta-analysis. J Am Med Dir Assoc. 2018 Mar;19(3):255-261.e1. https://doi.org/10.1016/j.jamda.2017.09.022
81. Maurer MS, Horn E, Reyentovich A, Dickson VV, Pinney S, Goldwater D, et al. Can a Left Ventricular Assist Device in Individuals with Advanced Systolic Heart Failure Improve or Reverse Frailty? J Am Geriatr Soc. 2017 Nov;65(11):2383-90. https://doi.org/10.1111/jgs.15124
82. Jaiswal A, Gadela NV, Baran D, Balakumaran K, Scatola A, Radojevic J, et al. Clinical outcomes of older adults listed for heart transplantation in the United States. J Am Geriatr Soc. 2021 Sep;69(9):2507-17. https://doi.org/10.1111/jgs.17271
83. Potapov EV, Antonides C, Crespo-Leiro MG, Combes A, Färber G, Hannan MM, et al. 2019 EACTS Expert Consensus on long-term mechanical circulatory support. Eur J Cardiothorac Surg. 2019 Aug 1;56(2):230-70. https://doi.org/10.1093/ejcts/ezz098
84. Lo Coco V, De Piero ME, Massimi G, Chiarini G, Raffa GM, Kowalewski M, et al. Right ventricular failure after left ventricular assist device implantation: a review of the literature. J Thorac Dis. 2021 Feb;13(2):1256-69. https://doi.org/10.21037/jtd-20-2228
85. Dew MA, DiMartini AF, Dobbels F, Grady KL, Jowsey-Gregoire SG, Kaan A, et al. The 2018 ISHLT/APM/AST/ICCAC/STSW recommendations for the psychosocial evaluation of adult cardiothoracic transplant candidates and candidates for long-term mechanical circulatory support. J Heart Lung Transplant. 2018 Jul;37(7):803-23. https://doi.org/10.1016/j.healun.2018.03.005
86. Magid M, Jones J, Allen LA, McIlvennan CK, Magid K, Thompson JS, et al. The Perceptions of Important Elements of Caregiving for a Left Ventricular Assist Device Patient: A Qualitative Meta-Synthesis. J Cardiovasc Nurs. 2016 May;31(3):215-25. https://doi.org/10.1097/JCN.0000000000000242

87. Lima B, Bansal A, Abraham J, Rich JD, Lee SS, Soleimani B, et al. Controversies and Challenges of Ventricular Assist Device Therapy. Am J Cardiol. 2018 May;121(10):1219-24. https://doi.org/10.1016/j.amjcard.2018.01.034

88. Fried J, Sayer G, Naka Y, Uriel N. State of the Art Review: Evolution and Ongoing Challenges of Left Ventricular Assist Device Therapy. Struct Heart. 2018 Jul;2(4):262-73. https://doi.org/10.1080/24748706.2018.1468125

89. von Schwarz ER, He M, Bharadwaj P. Palliative Care Issues for Patients With Heart Failure. JAMA Netw Open. 2020 Feb 26;3(2):e200011. https://doi.org/10.1001/jamanetworkopen.2020.0011

90. Lowey SE. Palliative Care in the Management of Patients with Advanced Heart Failure. Adv Exp Med Biol. 2018:1067:295-311. https://doi.org/10.1007/5584_2017_115

91. Rogers JG, Patel CB, Mentz RJ, Granger BB, Steinhauser KE, Fiuzat M, et al. Palliative Care in Heart Failure. J Am Coll Cardiol. 2017 Jul;70(3):331-41. https://doi.org/10.1016/j.jacc.2017.05.030

92. Sahlollbey N, Lee CKS, Shirin A, Joseph P. The impact of palliative care on clinical and patient-centred outcomes in patients with advanced heart failure: a systematic review of randomized controlled trials. Eur J Heart Fail. 2020 Dec;22(12):2340-6. https://doi.org/10.1002/ejhf.1783