Godina 2017. u kardiologiji: zatajivanje srca

The year in cardiology 2017: heart failure

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Uvod

Smjernice Europskoga kardiološkog društva (ECS) za zatajivanje srca (HF) iz 2016. godine stavile su u prvi plan nove preporuke za liječenje HF-a sa sniženom istisnom frakcijom (HFrEF; EF < 40 %). Uveden je novi pojam: HF s umjereno sniženom istisnom frakcijom (HFmrEF) za prije opisivanu „sivu zonu" u području istisne frakcije 40 – 49 %. Smjernice ističu i dalje prisutan nedostatak terapijskih mogućnosti zasnovanih na dokazima za HFmrEF i HF s očuvanom istisnom frakcijom (HFpEF, EF ≥ 50 %). Uvodi se koncept rane intervencije kod akutnog HF-a (AHF). Ovdje su sažeti podatci od jeseni 2016. do jeseni 2017. godine kojima su analizirani implementacija i korištenje postojećim terapijskim opcijama dokazano djelotvornima kod HFrEF-a, dodatna istraživanja koja su imala neutralne rezultate u HFpEF-u, ali s detaljnom karakterizacijom i potencijalnim terapijskim koristima u HFmrEF-u, razočaravajući rezultati istraživanja u AHF-u te rastući broj dokaza o koristima liječenja komorbiditeta.

Preamble

The 2016 European Society of Cardiology (ESC) heart failure (HF) guidelines brought to the fore new recommendations for the management of HF with reduced ejection fraction (HFrEF; EF <40%); introduced a new term: HF with mid-range EF (HFmrEF) for the previously denoted 'grey area' corresponding to EF 40–49%; highlighted the continued lack of evidence based interventions in HFmrEF and HF with preserved EF (HFpEF; EF ≥50%); and introduced the concept of early intervention in acute HF (AHF). Here we summarize data from autumn 2016 to autumn 2017 that analyse implementation and utilization of existing proven therapy in HFrEF; additional neutral trials in HFpEF but detailed characterization of and potential efficacy of therapy in HFmrEF; further disappointing trials in AHF; and growing evidence in favour of treating comorbidities.

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Liječenje zatajivanja srca s reduciranom istisnom frakcijom: implementacija i optimalna uporaba postojeće terapije

MEDIKAMENTNA TERAPIJA

U posljednjih 30 godina svjedočili smo iznimnom nizu uspješnih randomiziranih istraživanja u HFrEF-u, kojima su u kliničku praksu uvedene mnogobrojne intervencije koje poboljšavaju simptome i kvalitetu života te smanjuju incidenciju hospitalizacija i/ili mortalitet zbog HF-a.[1,2] S obzirom na to da uspjeh čak i velikih istraživanja često ovisi o malom broju ishoda i tradicionalno je definiran statističkim P-vrijednostima, nedavno je uvedena nova mjera robusnosti (ili fragilnosti) rezultata kliničkih istraživanja. Indeks fragilnosti (FI; engl. *fragility index*) opisuje broj nedogađaja koji moraju postati događaji kako bi rezultat istraživanja *učinili* neznačajnim, pokazujući time broj bolesnika potreban kako bi istraživanje iz statistički značajnog postalo neznačajno. Analiza 25 randomiziranih kontroliranih studija s medijanom broja bolesnika 2331 i primarnih ishoda 688, medijan FI bio je 26, a u trećini ispitivanja iznosio je manje od 10[3],*što sugerira* kako su istraživanja manje robusna nego što pretpostavljamo.

Unatoč tomu, najveća briga i dalje je činjenica da se postojeća terapija ne primjenjuje optimalno u kliničkoj praksi. Makar se inhibitori angiotenzin konvertirajućeg enzima (ACEi) / blokatori angiotenzinskih receptora (ARB) te beta-blokatori primjenjuju u 80 – 90 % bolesnika s HFrEF-om, doziranje je suboptimalno, što je povezano s višom smrtnosti i učestalošću hospitalizacija zbog HF-a.[4] Nedavno publicirani podatci iz *ESC HF Long-Term Registry* (iz odabranih europskih centara) navode kako se antagonisti mineralokortikoidnih receptora (MRA) rabe u samo dvije trećine bolesnika s HFrEF-om[5,6], a, prema neselektivnom *Swedish HF Registry*, u manje od trećine bolesnika.[7] Kronična bubrežna bolest i hiperkalijemija česti su u HF-u[8], a razlog za nedovoljno propisivanje MRA jest bojazan od hiperkalijemije i pogoršanja bubrežne funkcije.[9] Uvođenje novijih lijekova poput ivabradina ili sakubitril/valsartana odgađa se zbog inercije kliničara, premda je korist od njihove primjene dokazana neovisno o trajanju srčanog zatajivanja[10] te vrlo rano nakon uvođenja.[11]

Kako poboljšati primjenu navedenih lijekova? Jedna privlačna strategija jest nadzor, međutim, pojačani nadzor primjenom kućnih posjeta i strukturirane telefonske potpore nije smanjio broj ponavljajućih hospitalizacija, smrtnost ili troškove.[12] Dugo iščekivana studija GUIDE-IT, u kojoj su uspoređene strategija liječenja praćenjem vrijednosti NT-proBNP (ciljna vrijednost <1000 ng/L) i uobičajena skrb, nije rezultirala redukcijom kardiovaskularnih smrti, a ni prvih ili ukupnoga broja hospitalizacija zbog HF-a, kao ni smanjenjem vrijednosti NT-proBNP-a.[13] U studiji REM-HF praćenje nekih vitalnih parametara na daljinu s pomoću implantiranih uređaja nije rezultiralo poboljšanjem ishoda.[14] U studiji MultiSENSE primjena algoritma *HeartLogic* s pomoću ugrađenih uređaja predviđalo je dekompenzacije HF-a[15], međutim, tek se mora dokazati poboljšava li ishode.

Druga strategija uključuje poboljšanje organizacije i prioriteta liječenja. Primjena uređaja iznimno je varijabilna, no u konačnici nedovoljno iskorištena.[7] Makar korist od primjene resinkronizacijskog liječenja (CRT, engl. *cardiac resynchronization therapy*) nije smanjena komorbiditetima[16], evidentno

Heart failure with reduced ejection fraction treatment: implemetation and optimal utilization of existing therapy

DRUG THERAPY

The last 30 years have seen a remarkable series of successful randomized trials in HFrEF, which have brought to clinical use multiple interventions that improve symptoms and quality of life and reduce HF hospitalization and/or mortality.[1,2] While success of even large-scale outcome trials often depend on a small number of events and has been traditionally defined by statistical *P*-values, a novel measure of the robustness (or fragility) of the results of a clinical trial has been recently introduced. The fragility index (FI) describes the number of non-events that need to become events in order to render a trial result non-significant thus indicating how many patients would be required to convert a trial from being statistically significant to not significant. In a humbling analysis of 25 randomized controlled trials (RCT) with median sample size 2331 and primary events 688, the median FI was 26, and it was less than 10 in one-third of trials,[3] suggesting they may be less robust than we commonly assume.

Nevertheless, a greater concern is that existing therapy is not optimally utilized in the real world. Although angiotensin-converting enzyme inhibitors (ACEi)/angiotensin receptor blockers (ARBs) and β-blockers appear to be used in 80–90% of patients with HFrEF even in real-world settings, dosing is sub-optimal, which is associated with higher mortality and HF hospitalization.[4] Recent data from the ESC HF Long-Term Registry (selected European sites) suggest that mineralocorticoid receptor antagonists (MRAs) are used in only two-third of patients with HFrEF[5,6] and in the non-selective Swedish HF Registry, in less than one-third.[7] Chronic kidney disease and hyperkalaemia are common in HF[8] and reasons for MRA under-use appear to be perceived risk of or actual hyperkalaemia and worsening renal function.[9] More novel drugs such as ivabradine and sacubitril/valsartan may be deferred due to clinician inertia, even though they have demonstrated benefit regardless of HF duration[10] and very early after initiation.[11]

How can appropriate utilization be improved? One appealing strategy is monitoring. However, intensified management using home visits and structured telephone support did not reduce recurrent hospitalization, mortality or costs.[12] In the large and much anticipated Guiding Evidence Based Therapy Using Biomarker Intensified Treatment in Heart Failure (GUIDE-IT) trial a strategy of aiming for an NT-proBNP <1000 ng/L vs. usual care did not reduce cardiovascular (CV) death or first or total HF hospitalizations, or even NT-proBNP levels.[13] In Remote Management of Heart Failure Using Implantable Electronic Devices (REM-HF), remote monitoring using implantable devices did not improve outcomes.[14] In the MultiSENSE study, the HeartLogic algorithm using implantable device data predicted HF decompensation[15] but has still to be shown to improve outcomes.

Another strategy concerns improving the organization and prioritization of care. The use of devices is highly variable but overall underutilized.[7] Although, cardiac resynchronization therapy (CRT) benefit does not appear compromised by comorbidity burden,[16] it is conceivable that older and comorbid patients are less prioritized. In Sweden, non-use appears due

se manje primjenjuje u starijih i bolesnika s komorbiditetima. U Švedskoj se uzrokom rjeđe primjene ove vrste liječenja smatra slabija dostupnost specijalista kardiologa, više nego kliničkih obilježja.[17] U međunarodnom registru QUALIFY praćenje smjernica bilo je povezano s boljim ishodima.[18] Veliko švedsko istraživanje pokazalo je 35 % manji rizik od smrti u bolesnika uključenih u neobvezni registar *Swedish Heart Failure Registry*, a navedeno se pripisuje većoj primjeni optimalne medikamentne terapije u bolesnika uključenih u registar.[19]

UREĐAJI ZA LIJEČENJE SRČANOG RITMA

Implantabilni kardioverterski defibrilatori (ICD) i CRT uređaji poboljšavaju ishode u pojedinih bolesnika s HFrEF-om, što je dokazno mnogobrojnim randomiziranim kliničkim istraživanjima. Unatoč ovim nedavnim uspjesima, znatan broj bolesnika liječenih ICD i/ili CRT uređajem neće imati koristi od ove vrste liječenja, zbog čega se ističe važnost ispravnog probira. Duže trajanje QRS kompleksa, morfologija bloka lijeve grane i niža istisna frakcija lijeve klijetke i dalje su najvažniji indikatori odgovora na resinkronizacijsko liječenje.[20,21] U istraživanju RESPOND-CRT, u slučaju neadekvatnog odgovora na resinkronizacijsko liječenje rađene su ehokardiografski vođene optimizacije atrioventrikulskih (AV) i ventrikuloventrikulskih (VV) intervala.[22] Primjena multimodalnih metoda kardiološkog oslikavanja u svrhu optimalnog pozicioniranja elektrode te isključivo lijevostrane stimulacije mogu povećati odgovor na resinkronizacijsko liječenje.[23-25] Međutim, uzevši u obzir velik broj parametara uključenih u odgovor na CRT i ishode, predviđanje odgovora na CRT i dalje je nedostižno te je moguće da potencijalni smjer za buduća istraživanja leži u većim multiparametrijskim pristupima s velikim podatcima.[26,27]

Smjernice ESC-a iz 2016. godine preporučuju ugradnju ICD-a u svrhu primarne prevencije u bolesnika s ishemijskom i neishemijskom kardiomiopatijom.1 Ovo istražuje studija DANISH[28], gdje je primarna prevencija ugradnjom ICD uređaja u bolesnika s neishemijskom kardiomiopatijom smanjila incidenciju iznenadne srčane smrti, no ne i ukupne smrtnosti. U sekundarnoj analizi povezanost između ugradnje ICD-a i preživljenja smanjivala se s dobi, a dobna granica od 70 godina označivala je najveću stopu preživljenja za ukupnu populaciju.[29] Nadalje, neopravdani šokovi u vezi s ICD uređajima učestaliji su kod bolesnika s težim oblikom HF-a.[30] S druge strane, nekoliko prošlogodišnjih metaanaliza upućuje na znatan pad i u iznenadnoj srčanoj smrti i u ukupnoj smrtnosti[31-34]. Moguće je kako su bolesnici u navedenim studijama imali manje učinkovitu medikamentnu terapiju. Dapače, analiza 12 kliničkih ispitivanja upućuje na snizivanje učestalosti iznenadne smrti to poor access to cardiology specialists rather than clinical variables.[17] In the international QUALIFY registry, guideline adherence was associated with improved outcomes.[18] A large Swedish study showed that enrolment vs. non-enrolment in the non-selective but voluntary Swedish Heart Failure Registry was associated with a 35% lower risk of death, and that the strongest explanatory factor was greater use of HF and CV medications in patients enrolled in the registry.[19]

CARDIAC RHYTHM MANAGEMENT DEVICES

Implantable cardioverter-defibrillators (ICDs) and CRT improve outcomes in selected patients with HFrEF in multiple randomized clinical trials. These recent successes notwithstanding, a substantial number of patients receiving an ICD and/or CRTs do not benefit from the device thus highlighting the need for improvement in patient selection. Longer QRS duration, left bundle branch block morphology, and lower LVEF remain the most important independent predictor of response to CRT.[20,21] In the RESPOND-CRT trial, non-response was ameliorated by an echo-guided optimization of atrioventricular (AV) and ventriculoventricular (VV) intervals.[22] Multimodality cardiac imaging strategies for lead placement, and possibly, left ventricular-only pacing, may increase CRT response.[23–25] But given the many factors involved in CRT response and outcomes, predicting CRT response remains elusive and the potential for larger multi parametric big-data approaches should be considered for future trials.[26,27]

The 2016 ESC guidelines recommend primary prevention ICD in both ischaemic and non-ischaemic cardiomyopathy.[1] This was called into doubt by DANISH,[28] where primary prevention ICD in non-ischaemic cardiomyopathy reduced sudden cardiac death but not all-cause death. In a secondary analysis, the association between ICD and survival decreased with age, and a cut-off of 70 years was suggested to yield the highest survival for the population as a whole.[29] Furthermore, inappropriate ICD therapy appears more likely in patients with more severe HF.[30] At the same time, in the last year, several meta-analyses point to a distinct reduction in both sudden and all-cause death.[31–34] Patients in these meta-analyses may have had less effective medical therapy than contemporary patients. Indeed, a large analysis form 12 clinical trials suggested that the rates of sudden death have declined over time (**Figure 1**),[35] which would be consistent with potentially lower benefit of primary prevention ICD in patients with contemporary treatment. Furthermore, benefits may differ substantially depending on e.g. age[28] and concomitant use of CRT, and in several recent studies multivariable prediction models

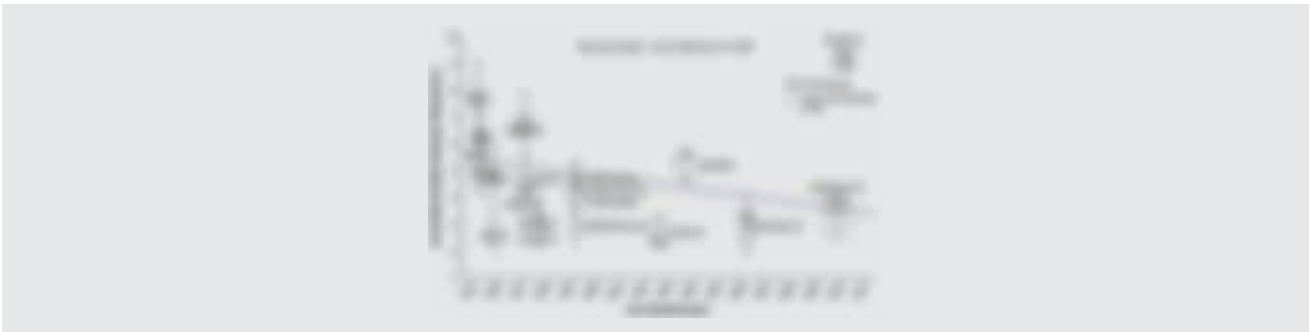

FIGURE 1. Rates of sudden death per 100 patient-years in heart failure with reduced ejection fraction trials.

nosti (**slika 1**)[35], što je sukladno s potencijalno nižom koristi ICD-a u svrhu primarne prevencije u bolesnika sa suvremenom terapijom. Nadalje, navedena korist može znatno varirati ovisno o životnoj dobi[28] i istodobnoj primjeni resinkronizacijske terapije, a u nekoliko nedavnih studija multivarijatni predikcijski modeli primijenjeni su kako bi bolje predviđali naglu srčanu smrt i korist od ugradnje ICD uređaja.[36-38]

Zatajivanje srca s očuvanom istisnom frakcijom

I dalje je kontroverzno pitanje je li HF s očuvanom istisnom frakcijom (HFpEF) varijanta HFrEF-a, odvojeni entitet ili, jednostavno, posljedica starenja i povezanih komorbiditeta. HFpEF je povezan s nižim kardiovaskularnim rizikom nego HFrEF, no nedvojbeno je kako je u stvarnome svijetu ukupna smrtnost jednaka onoj u bolesnika s HFrEF-om, uz brzo rastuću prevalenciju.[1] Ranije studije s ACEi, ARB-ovima i nitratima bile su razočaravajuće.[1] Nedavno u studiji EDIFY primjena ivabradina nije poboljšala šestominutni test hoda (6MWT), vrijednost NT-proBNP, ni E/e'.[39] U studiji TOPCAT spironolakton se nije pokazao učinkovitim[40], no regionalne analize pokazale su mogući učinak u Sjevernoj i Južnoj Americi.[41] Pozitivan učinak spironolaktona uočen je u populaciji ispitanika stratificiranima prema vrijednostima NT-proBNP-a u kojih je potvrđen HF.[42] Zanimljivo, u studijama TOPCAT i I-PRESERVE liječenje je bilo učinkovitije u bolesnika s nižim vrijednostima natriuretskih peptida.[43-45] Navedeno uzrokuje poteškoće pri dizajniranju studija – s jedne strane, inzisitranjem na povišenim vrijednostima natriuretskih peptida osigurava se prisutnost HF-a u ispitanika, no moguće je kako je pri znatno povišenim vrijednostima bolest manje podložna terapijskim intervencijama. U planu je reevaluacija uloge antagonista mineralokortikoidnih receptora u velikoj studiji koja će uključivati bolesnike s HFpEF-om i HFmrEF-om.[46]

Zatajivanje srca s umjereno sniženom istisnom frakcijom

Smjernice ESC-a iz 2016. uvele su novi pojam HF s umjereno sniženom istisnom frakcijom (engl. *heart failure with mid-range ejection fraction* – HFmrEF), koji odgovara ranijoj takozvanoj sivoj zoni s EF-om 40 – 49 %.[1] Međutim, EF nije idealni parametar za klasificiranje HF-a, a također je s vremenom i liječenjem podložan promjenama.[47] Nedavna je studija pokazala da je poboljšanjem EF-a čak 17 – 34 % bolesnika s HFrEF-om ili HFmrEF-om bilo preklasificirano u višu grupu. Kako se i očekivalo, to se češće događalo u bolesnika s neishemijskom bolesti srca.[48] Poboljšanju klasifikacije HF-a mogu pomoći i drugi parametri, poput ehokardiografskih analiza deformacija miokarda, posebice globalnoga longitudinalnog straina.[49,50] Ipak potrebno je još vidjeti koliko će njihova primjena zaživjeti u svakodnevnoj kliničkoj praksi. S obzirom na heterogenost i teškoće pri klasificiranju HF-a, posebno onog s očuvanim EF-om, poboljšanje njegova definiranja postiže se primjenom individualnog pristupa utemeljenog na više čimbenika. Sličan se sustav već primjenjuje u onkologiji.[27,51]

Za klasifikaciju HF-a ipak se i dalje najčešće uporabljuje EF. Činjenica je da EF od 40 do 49 % nije normalna, ali da još uvijek za tu skupinu koja uključuje više od 20 % bolesnika s HF-om[52,53] ne postoji na dokazima temeljena terapija. Stoga su potrebna daljnja klinička istraživanja.[1] Više radova tijekom prošle godine upućuje na to da, osim umjereno snižene were used to refine sudden death risk prediction and ICD benefit.[36–38]

Heart failure with preserved ejection fraction

Controversy remains as to whether HFpEF is a variant of HFrEF, a distinct entity, or merely a consequence of ageing and related comorbidities. It is associated with lower CV risk than HFrEF but it is indisputable that in the real world, it has the same overall mortality as HFrEF and is increasing more rapidly in prevalence.[1] Previous trials of ACEi, ARBs, and nitrates have been disappointing.[1] Recently, in EDIFY, ivabradine did not improve 6MWT, NT-proBNP, or E/e'.[39] In Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT), spironolactone was overall not effective[40] but regional analyses suggested a potential effect in North and South America.[41] Perhaps more importantly, in the pre-specified stratum including patients based on NT-proBNP levels, consistent with confirmed HF, spironolactone was effective.[42] Interestingly, in both TOPCAT and I-PRESERVE, treatment was more effective in patients with lower natriuretic peptide levels.[43–45] So as we struggle in HFpEF trial design to ensure presence of HF and to enrich for HF events by requiring elevated NPs, as NPs go too high, the syndrome may be less amenable to intervention. Now, MRAs will be reassessed in a large pragmatic trial including patients with both HFpEF and HFmrEF.[46]

Heart failure with mid-range ejection fraction

The 2016 ESC guidelines introduced a new term HFmrEF, corresponding to the previously denoted 'grey area' EF 40–49%.[1] However, EF is not an ideal marker to classify HF, and EF may change with treatment and time.[47] A recent study suggested that 17-34% of patients with HFrEF or HFmrEF improve to a higher category, and that this, as expected, was more common in the absence of ischaemic heart disease.[48] Other modalities may refine characterization of HF, such as global longitudinal strain,[49,50] but their impact in clinical routine remains to be seen. Given the heterogeneity of HF and difficulty characterizing HF, in particular with preserved EF, multimarker personalized approaches to HF, as occurs in oncology, may improve characterization and classification in HF.[27,51]

But EF remains the most commonly used classifier and the fact remains: EF 40–49% is not normal but there is no evidence based therapy, and further research is needed in this group,[1] comprising more than 20% of patients with HF.[52,53] Extensive work during the last year suggest that although HFmrEF may be intermediate regarding some characteristics,[54–57] it resembles HFrEF regarding age, preponderance of male sex, greater prevalence of ischaemic heart disease[48] and greater prognostic impact of chronic kidney disease.[52] Recent studies also suggest that standard HF therapy may be effective in HFmrEF. In an individual patient-level meta-analysis from RCTs, β-blockers were not effective in atrial fibrillation (AF), but in sinus rhythm, they reduced all-cause and CV mortality in HFrEF and HFmrEF but not HFpEF (**Figure 2**).[58] Similarly, in a *posthoc* analysis from Candesartan in Heart failure – Assessment of moRtality and Morbidity (CHARM), candesartan reduced the composite of CV death and HF hospitalization in HFrEF (where 57% received concomitant ACEi), and HFmrEF (27% ACEi) but not HFpEF (16% ACEi).[59] Currently, drugs rec-

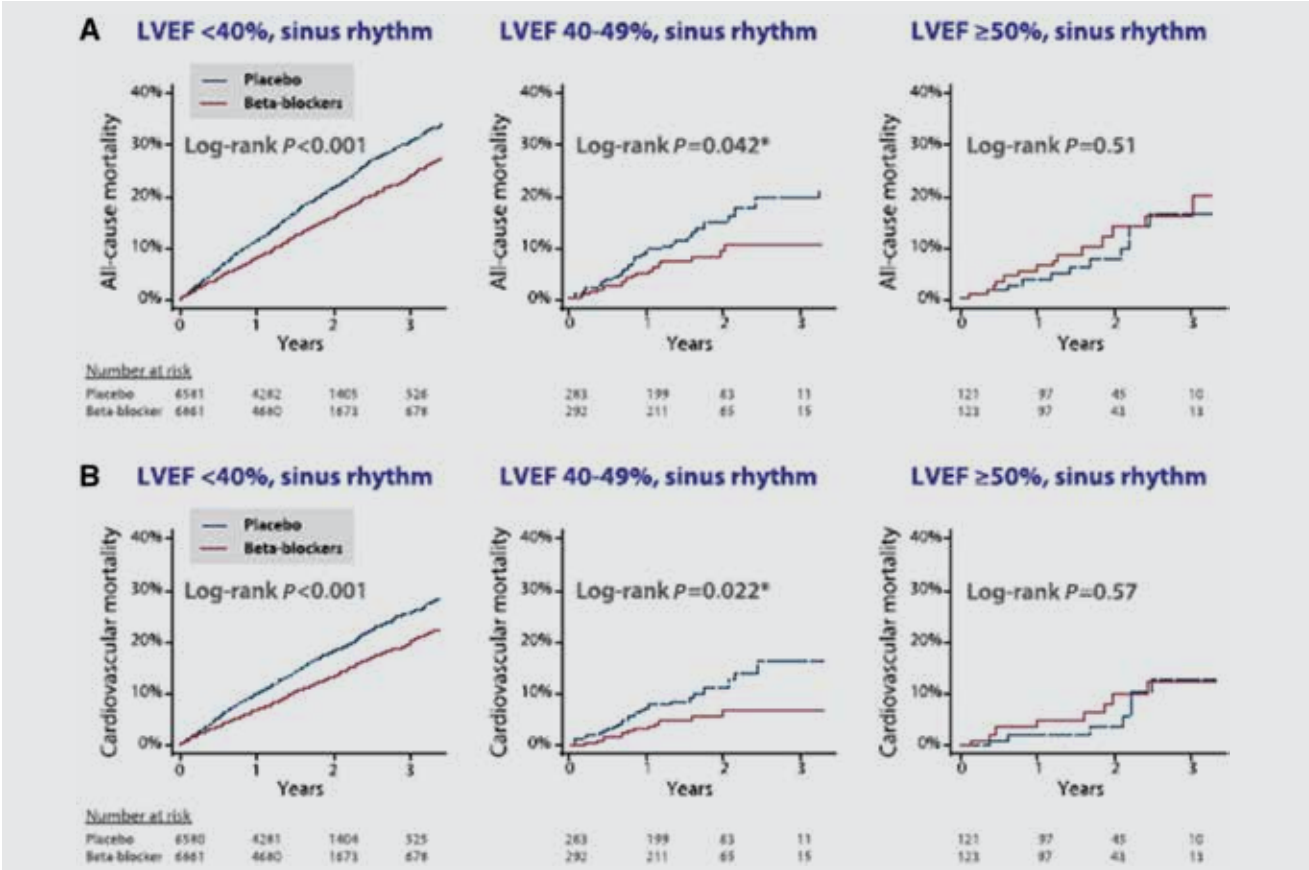

FIGURE 2. All-cause mortality (*A*) and cardiovascular mortality (*B*) in patients with sinus rhythm and heart failure with different ejection fraction categories treated with β-blockers vs. placebo. From an individual patient-level analysis of double-blind randomized trials.[58]

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ne EF, HFmrEF s više obilježja sliči HFrEF-u[54-57], a to su dob bolesnika, prevalencija muškog spola, veća učestalost ishemijske bolesti srca[48] i značajni prognostički učinak kronične bolesti bubrega.[52] Nedavne studije također upućuju na to da standardna terapija HF-a može biti učinkovita i u bolesnika s HFmrEF-om. Prema metaanalizi randomiziranih kontroliranih studija, beta-blokatori se nisu pokazali učinkovitima u bolesnika s fibrilacijom atrija, ali su u onih sa sinusnim ritmom smanjili ukupnu i kardiovaskularnu smrtnost kod HFrEF-a i HFmrEF-a, ali ne i kod HFpEF-a (**slika 2**).[58] Slično tomu, u *post hoc* analizi studije CHARM kandesartan je smanjio kombiniranu kardiovaskularnu smrtnost i broj hospitalizacija bolesnika s HF-om i HFrEF-om (57 % primalo je istodobno i ACEi) i HFmrEF-om (27 % na ACE-i), ali ne i kod HFpEF-a (16 % na ACE-i).[59] Trenutačno, iako ovi podatci upućuju na to da bi mogli biti učinkoviti, lijekovi preporučeni u HFrEF-u ne preporučuju se i u HFmrEF-u. Potrebne su nove pragmatične studije kojima bi se utvrdila njihova učinkovitost.[46]

Komorbiditeti

U bolesnika sa šećernom bolesti SGLT2 inhibitori tek blago smanjuju HbA1c. Ipak je njihova primjena u kliničkim studijama smanjila učestalost hospitalizacija ispitanika zbog

ommended in HFrEF are not recommended in HFmrEF, but these data suggest that they may be effective, and novel pragmatic trials should test this hypothesis.[46]

Comorbidities

In diabetes mellitus, SGLT2 inhibitors modestly lower HbA1c. But in EMPA-REG (10% HF at baseline), empagliflozin reduced HF hospitalization by 35%,[60] and in CANVAS (14% HF at baseline), canagliflozin reduced HF hospitalization by 33%.[61] This has generated considerable interest in SGLT2 and also SGLT2/1 inhibition in HF[62,63] and several trial programs are underway[64] to address whether SGLT2/1 inhibitors in combination with diuretics can improve outcomes in prevalent HF, with HFrEF, HFmrEF, and/or HFpEF, and with and without diabetes.

Recent real-world data suggest that AF is more common in HF than previously believed, at 53% in HFrEF, 60% in HFmrEF and 63% in HFpEF in one generalizable study.[54] In CASTLE-AF, catheter ablation in patients with HFrEF (EF <35%) and paroxysmal or persistent AF appeared to reduce combined HF hospitalization and all-cause mortality[65] although these result have not yet been published. In RACE 3, in patients with

HF-a. Tako su, prema studiji EMPA-REG (10 % bolesnika na početku je imalo HF), primjenom emfaglifozina hospitalizacije zbog HF-a smanjene za 35%,[60] a u studiji CANVAS (14 % HF-a na početku) primjenom kanagliflozina za 33 %.[61] To je izazvalo znatan interes za SGLT2 i SGLT2/1 inhibiciju u ZS-u[62,63] i trenutačno je u tijeku nekoliko studija[64] kako bi se utvrdilo mogu li inhibitori SGLT2/1 u kombinaciji s diureticima poboljšati ishode u prevalenciji HF-a, bilo u bolesnika s HFrEF-om, HFmrEF-om i/ili HfpEF-om te sa šećernom bolesti ili bez nje.

Nedavni podatci iz kliničke prakse te jedne populacijske studije pokazuju da je FA s incidencijama od 53 % u HFrEF-u, 60 % u HFmrEF-u i 63 % u HFpEF-u učestalija u HF-u nego što se prije vjerovalo.[54] U studiji CASTLE-AF u bolesnika s HFrEF-om (EF <35 %) i paroksizmalnom ili postojanom FA-om, iako ti rezultati još nisu objavljeni, čini se da je liječenje kateterskom ablacijom smanjilo učestalost hospitalizacija zbog HF-a i ukupnu smrtnost. U studiji RACE 3 u bolesnika s HF-om i trajnom FA koji su podvrgnuti električnoj kardioverziji, istodobna kardiovaskularna rehabilitacija i primjena medikamentne terapije statinom, ACE-i ili ARB-a i MRA rezultira održavanjem sinusnog ritma kroz godinu dana u 75 % bolesnika, u odnosu prema 63 % s uobičajenim liječenjem.[66]

Čak polovica bolesnika s HFrEF-om, bez obzira na to jesu li anemični ili nisu, ima nedostatak željeza.[67] Nedavne studije na životinjama upućuju na to da to nepovoljno utječe na rad mitohondrija kardiomiocita i smanjuje mogućnost prilagodbe povećanju srčanog opterećenja.[68] Liječenje intravenskim željezom rezultira znatnim poboljšanjima u 6MWT i kvaliteti života, a metaanaliza sugerira da također smanjuje učestalost hospitalizacija zbog HF-a.[69] Iako bi bilo bolje bolesnike liječiti oralnim, a ne intravenskim željezom, njegova je bioraspoloživost niska. Velika studija IRONOUT-HF pokazala je da peroralno željezo ne poboljšava vršnu vrijednost VO_2, 6MWT, KCCQ skor, kao niti serumsku razinu NTproBNP-a.[70]

Akutno zatajivanje srca

Na osnovi koncepta akutnoga koronarnog sindroma „vrijeme je mišić",[1] prva prezentacija AHF-a može predočivati razdoblje znatne osjetljivosti miokarda.[71] Predloženo je stoga da se što ranijom intervencijom intravenskim vazodilatatorom smanje opterećenje stijenki i daljnje oštećenje miokarda te u konačnici poboljša dugoročna prognoza bolesnika s AHF-om.[71]

S druge strane, liječenje ularitidom s medijanom od 6 sati u TRUE-AHF, randomiziranoj, dvostruko slijepoj, placebom kontroliranoj i događajima vođenoj studiji, s paralelnom grupom, nije smanjilo nepovoljne zajedničke ciljne ishode u prvih 48 sati liječenja kao ni 15-mjesečnu smrtnost od KV-a.[72] Slično tomu, i rano davanje serelaxina u RELAX-AHF2 studiji nije utjecalo na poboljšenje HF-a unutar 5 dana ili smrti od KV-a tijekom 6 mjeseci.[73] Zanimljivo, opservacijska studija upućuje na to da je liječenje diureticima Henlejeve petlje unutar 1 sat od dolaska u hitnu službu povezano s nižom smrtnosti tijekom hospitalizacije[74], ali opažajna priroda te studije isključuje sve zaključke o optimalnom tipu ili vremenu intervencija u AHF-u.

U studiji BLAST-AHF selektivni ligand za tip 1 angiotenziskih II receptora nije smanjio učestalost zaduhe, HF ili dužinu boravka u bolnici.[75] Još jedan koncept jest rana inhibicija aldosterona, ali u studiji ATHENA-HF 100 mg spironolaktona u usporedbi s placebom nije poboljšalo razine natriuretskih peptida ili kliničke pokazatelje.[76] Do kraja 2017. godine više studija s raznim intervencijskim strategijama u AHF-u po-

HF and persistent AF who underwent electrical cardioversion, a concomitant strategy of cardiac rehabilitation, statins, an ACEi or ARB, and an MRA, resulted in maintained sinus rhythm at 1 year in 75% of patients, compared with 63% in the usual care group.[66]

Iron deficiency affects as many as half of patients with HFrEF, irrespective of anaemia,[67] and recent animal studies suggest that this occurs through impaired cardiomyocyte mitochondrial respiration and adaptation to increases in workload.[68] Intravenous iron treatment results in considerable improvements in 6MWT and quality of life, and a meta-analysis suggest that it also reduced HF hospitalization.[69] It would be appealing to treat with oral rather than intravenous iron, but bioavailability is low and the large IRONOUT-HF trial showed that oral iron did not improve peak VO_2, 6MWT, KCCQ score, or NT-proBNP levels.[70]

Acute heart failure

On the basis of the ACS concept of 'time is muscle',[1] the initial presentation of acutely decompensated HF may represent a period of substantial myocardial vulnerability.[71] As such, the early intervention with an intravenous vasodilator has been proposed as a therapeutic goal to reduce cardiac-wall stress and myocardial injury, and ultimately long-term prognosis in patients with AHF.[71]

In the TRUE-AHF trial, a randomized, double-blind, parallel-group, placebo-controlled, event-driven trial, however, ularitide given at a median of 6 h after evaluation did not reduce the composite endpoint of 48 h clinical course and 15 month CV mortality.[72] Similarly, early administration of serelaxin did not improve the composite endpoint of worsening HF at 5 days or CV death at 6 months in RELAX-AHF2.[73] Interestingly, an observational study suggested that treatment with intravenous loop diuretic within 1-h of presentation to the emergency department was associated with lower in-hospital mortality,[74] but the observational nature of this study precludes any conclusions regarding optimal type or timing of AHF interventions.

In BLAST-AHF, a biased ligand of the angiotensin II type 1 receptor did not reduce dyspnoea, worsening HF or hospital length of stay.[75] Another concept is early aldosterone inhibition, but in ATHENA-HF, 100 mg of spironolactone compared to placebo did not improve natriuretic peptides or clinical measures.[76] Thus by end of 2017, numerous interventional strategies in AHF have failed, including continuous diuretics infusion, ultrafiltration, vasodilators and inotropes.

Advanced heart failure

In patients with severe refractory symptoms despite optimal medical management, quality of life and prognosis are dismal. The remaining options include heart transplantation (HTx), durable mechanical circulatory support (MCS), and palliation. After 30 years of remarkable success of HFrEF drug trials,[1,2] it is notable that In 2017 we celebrate 50 years since the first HTx performed in 1967, and indeed the establishment of HTx as an option paved way for the worldwide HF referral centres and research programs that brought us the subsequent advances in HF pharmacotherapy.

kazale su se neuspješnima, uključujući kontinuiranu infuziju diuretika, ultrafiltraciju, vazodilatatore i inotrope.

Uznapredovalo zatajivanje srca

U bolesnika s teškim i refraktarnim simptomima kvaliteta života i prognoza loši su unatoč optimalnom liječenju. Preostale opcije uključuju transplantaciju srca (engl. *heart transplantation*, HTx), trajnu mehaničku cirkulacijsku podršku (engl. *mechanical circulatory support*, MCS) i simptomatsko palijativno liječenje. Nakon 30 godina izvanrednih uspjeha farmakoloških studija u liječenju HFrEF-a[1,2] važno je i to da u 2017. godini slavimo 50 godina od prve HTx učinjene 1967. godine. Već je i sam razvoj HTx-a doveo do stvaranja niza referentnih centara za HF diljem svijeta, kao i razvoja istraživačkih programa koji pogodovali daljnjem napretku u farmakoterapiji.

Slično tomu, uređaji za cirkulatornu potporu lijevom ventrikulu (engl. *left ventricular assist devices*, LVADs) uvedeni su u kliničku praksu već 60-ih godina prošloga. Posljednjih godina rezultati HTx[77] i implantacije LVAD-ova, bilo kao prijelazno rješenje prije transplantacije bilo kao definitivno liječenje[78] znatno poboljšani. Međutim, i dalje su prisutne komplikacije nakon HTx-a, a kliničke studije pokazuju potrebu za individualiziranijim pristupom u imunosupresivnoj terapiji.[79] Broj se izvedenih HTx-a smanjuje[77], a broj se implantiranih LVAD-a, s druge strane, tek skromno povećava.[78] Usprkos znatnoj redukciji smrtnosti, primjena LVAD-ova još je uvijek ograničena komplikacijama. Čini se da moderni mali centrifugalni LVAD-ovi s kontinuiranim protokom smanjuju rizik od tromboze u uređaju[80], ali i dalje ostaje zabrinutost zbog veće incidencije moždanog udara, krvarenja, disfunkcije desne klijetke i infekcije kroz vanjske vodove za napajanje.

U ispitivanju PAL-HF-a interdisciplinarna palijativna skrb u usporedbi s uobičajenom skrbi pokazala je niz prednosti u poboljšanju kvalitete života i duhovnog blagostanja, smanjenju anksioznosti i depresije (**slika 3**).[81] Zbog nedostatka donorskih organa te još uvijek visokih troškova i čestih komplikacija trajnih MCS-a potreban je posebno pažljiv odabir bolesnika pogodnih za te metode liječenja, osim indikacija i moguće koristi, potrebno je sagledati i kontraindikacije te moguće rizike.

Novi oblici intervencijskog liječenja

Koliko kod se usredotočili na optimizaciju postojeće terapije, HF ostaje kronični, neizlječivi, uglavnom ireverzibilni te po-

Similarly, implantable left ventricular assist devices (LVADs) were introduced already in the 1960s. In recent years, outcomes with HTx[77] and with LVAD both as bridge to transplantation and as destination therapy[78] have improved worldwide. However, HTx is associated with complications and studies are suggesting immunosuppression should be more individualized.[79] The number of HTx procedures performed are stagnant[77] and LVAD use is increasing only modestly.[78] Despite remarkable effect on mortality, LVADs are still limited by complications. Modern small centrifugal continuous flow LVADs appear to reduce the risk of thrombosis in the device,[80] but concerns over stroke and bleeding, right ventricular failure, and infection through the external driveline remain.

In the PAL-HF trial, interdisciplinary palliative care compared with usual care showed benefits in quality of life, anxiety, depression, and spiritual well-being (**Figure 3**).[81] It is increasingly recognized that the scarcity of donor organs and the still high cost and complications with durable MCS demand especially careful selection, considering both indications and benefits as well as contraindications and risks.

Novel interventional strategies

As much as we need to focus on optimal utilization of existing therapy, HF remains a chronic, incurable, generally irreversible, and still debilitating syndrome, and novel inventive approaches have continued appeal. A new myosin activator which improves impaired contractility, omecamtiv mecarbil, was studied in the phase II study COSMIC-HF.[82] Titration guided by pharmacokinetics resulted in improved cardiac function and decreased NT-proBNP.[82] A Phase III trial is ongoing. Stem cell therapy has generally proven disappointing, but in the exploratory REGENERATE-IHD and CHART-1, intramyocardial injection of autologous bone-marrow derived cells in ischaemic cardiomyopathy appeared safe and improved EF, New York Heart Association (NYHA) class and NT-proBNP, and left ventricular (LV) end-systolic and diastolic volumes.[83–85] Novel radiocarbon (^{14}C) techniques allow assessment of cardiomyocyte turnover dynamics and may provide a future foundation for regenerative strategies.[86] The ESC Task Force for stem cells in myocardial infarction and HF[87] and a global position statement on cardiovascular regenerative medicine[88] outline challenges for the stem cell field, and standardization of animal models, clinical trials and regulatory procedures are put forth as necessary for future success.

FIGURE 3. In PAL-HF trial, palliative vas significantly superior to usual care in improving quality of life.

stupno progresivni sindrom, tako da postoji stalna potreba razvoja novih inventivnih pristupa liječenju. Za novi aktivator miozina omecamtiv mecarbil koji poboljšava oslabljenu kontraktilnost završena je COSMIC-HF, klinička studija faze II.[82] Titracija lijeka vođena farmakokinetikom rezultirala je poboljšanjem srčane funkcije i smanjenjem vrijednosti NT-proBNP-a.[82] Studija faze III. je u tijeku. Terapije matičnim stanica općenito su se pokazale razočaravajućima, ali u eksperimentalnim studijama REGENERAT-IHD i CHART-1 intramiokardijalno uštrcavanje autolognih stanica iz koštane srži u bolesnika s ishemijskom kardiomiopatijom pokazalo se sigurnim uz poboljšanje EF, New York Heart Association (NYHA) razreda, vrijednosti NT-proBNP, kao i volumena na kraju sistole te dijastoličkog volumena lijeve klijetke.[83-85] Nove metode s radioaktivnim ugljikom (^{14}C) omogućuju procjenu dinamike promjene kardiomiocita i mogu pružiti osnovu za razvoj budućih regenerativnih strategija.[86] Radna skupina ESC-a za primjenu matičnih stanica u infarktu miokarda i HF-u[87] te Izjava o globalnoj poziciji kardiovaskularne regenerativne medicine[88] postavili su osnovne izazove za primjenu matičnih stanica, kao i standardizaciju životinjskih modela, klinička ispitivanja i regulatorne postupke, što je sve potrebno za budući uspjeh terapije. Genetsko „uređivanje" ciljane grupe ponavljajućih umetnutih kratkih palindromskih ponavljanja (CRISPR) obećava, tehnika ima moguću široku primjenu npr. uređenje gena koji uzrokuju hipertrofijsku kardiomiopatiju još u ljudskim embrijima.[89]

Zaključak

Ovo je bila još jedna godina u kojoj je objavljeno više novih studija o HF-u. Međutim, nijedna od njih neće promijeniti postojeću kliničku praksu. Veliki izazov za liječnika kliničara jest osigurati da se bolesnici s HFrEF-om liječe u skladu sa smjernicama, a veliki je izazov također razvoj učinkovitih metode liječenja HFpEF-a i AHF-a.

Gene 'editing' targeting Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) is a promising technique with broad applications that has been used e.g. to edit hypertrophic cardiomyopathy causing genes in human embryos.[89]

Conclusions

This has been another year with many new trials reporting in HF. However, none of them will change clinical practise at present. A major challenge for the practising physician is to make sure that eligible patients with HFrEF receive guideline recommended care, and a major challenge for the HF community is to develop effective interventions in HFpEF and AHF.

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