# Godina 2020. u kardiovaskularnoj medicini: zatajivanje srca i kardiomiopatije

# The year in cardiovascular medicine 2020: heart failure and cardiomyopathies

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## Uvod

Prevalencija zatajivanja srca (HF) i dalje je visoka diljem svijeta, sa znatnim razlikama vezanima uz spol i regiju u učestalosti, liječenju i ishodima. U 2020. godini objavljeni su pozitivni pomaci uporabe biomarkera i slikovnih metoda za dijagnozu i prognozu dijastoličke disfunkcije, HF-a s očuvanom ejekcijskom frakcijom ili monitoriranja kardiotoksičnosti; objavljena je i nova definicija HF-a s oporavljenom ejekcijskom frakcijom lijeve klijetke (LVEF). Dobrobiti od primjene inhibitora reninsko-angiotenzinsko-aldosteronskog sustava i beta-blokatora mogli bi se proširiti na bolesnike s LVEF-om do 55 %. Sakubitril-valsartan je poboljšao remodelaciju lijeve klijetke, razinu biomarkera i stopu iznenadne srčane smrti.

## Introduction

Heart failure (HF) prevalence remains high worldwide with significant sex-related and regional differences in its presentation, management, and outcomes. In 2020, advances in biomarkers and imaging techniques were reported for the diagnosis and prognosis of diastolic dysfunction, HF with preserved ejection fraction or monitoring cardiotoxicity; a new definition of HF with recovered left ventricular ejection fraction (LVEF) was released. Benefits of renin–angiotensin–aldosterone system inhibitors and β-blockers may extend to patients with an LVEF up to 55%. Sacubitril–valsartan improved LV remodelling, biomarker levels, and rates of sudden cardiac death. Two studies investigating the

Objavljene su dvije studije koje su istraživale učinke inhibitora natrij-glukoza kotransporter 2 emfagliflozina i sotagliflozina u bolesnika s HF-om. Studija *EMPEROR-Reduced* u bolesnika s HF-om uz sniženu EF sa šećernom bolešću tipa 2 ili bez nje (T2DM) pokazala znatno smanjenje kardiovaskularnih (CV) smrti i učestalosti hospitalizacija zbog HF-a (HFH). U bolesnika s T2DM-om i HF-om uz spektar vrijednosti LVEF-a nakon aktualne hospitalizacije, studija *SOLOIST* pokazala je smanjenje primarnog zajedničkog ishoda (CV smrtnosti, ukupne HFH i hitnih pregleda zbog HF-a). Dodatno, u bubrežnih bolesnika, neovisno o prisutnosti šećerne bolesti (*DAPA-CKD*), dapagliflozin je prevenirao pogoršanje bubrežne funkcije. Dva novija lijeka, aktivator solubilne gvanilat ciklaze vericiguat i aktivator miozina omecamativ mekarbil, u velikim istraživanjima ishoda *VICTORIA* i *GALACTIC-HF* dominantno su smanjila HFH u visokorizičnih bolesnika s pogoršanjem HF-a. U studiji *AFFIRM-AHF* intravenska primjena željezove karboksimaltoze smanjila je HFH u bolesnika s manjkom željeza nakon dekompenzacije HF-a.

Godina 2020. bit će zapamćena kao godina bolesti uzrokovane koronavirusom (COVID-19). Pandemija uzrokovana teškim akutnim respiratornim sindromom koronavirusa 2 (SARS-CoV-2) imala je golem učinak na globalno zdravlje i ekonomiju. Kada ovaj članak bude objavljen, >80 milijuna osoba bit će zaraženo, a >1,75 milijuna ljudi će umrijeti od te bolesti. Velik će broj drugih osoba umrijeti ili će doći do pogoršanja njihovih bolesti, od kojih su u mnogih posrijedi CV bolesti, kao neizravan učinak straha izazvana traženja pomoći ili zbog kolapsa zdravstvenog sustava. Ipak, znanost i medicinska skrb nastavile su se razvijati tijekom godine. Ovaj članak daje osvrt na važne napretke u polju HF-a tijekom 2020. godine.

## Epidemiologija

U svijetu živi više od 64 milijuna ljudi s HF-om, s procijenjenom prevalencijom od 1 do 2 % odraslih u razvijenim zemljama, najčešće uz nekoliko komorbiditeta.[1] Incidencija HF-a možda se globalno stabilizira, uz smanjenje broja u zemljama s visokim prihodima,[2] ali se povećava u zemljama s niskim prihodima, pomiče prema HF-u s očuvanom ejekcijskom frakcijom (HFpEF), te povećava zbog starenja populacije i porasta učestalosti pretilosti.[1] Životna dob, tradicionalni čimbenik rizika za HF, sjedilački stil života i socijalna deprivacija povezani su s pojavnošću HF-a.[3] Zapravo, životni stil i socijalne odrednice zdravlja privlače sve više pažnju u epidemiologiji i skrbi bolesnika s HF-om.[4] U bolesnika s novootkrivenom HF-om najčešći prvi sljedeći događaji jesu srčani incident (36 %), ponavljajuća HF (28 %) ili smrt (29 %).[5]

Netradicionalni čimbenik rizika, kao što je to implantacija elektrostimulatora srca, može imati ulogu u razvoju HF-a: unutar prvih dviju godina nakon implantacije u bolesnika bez poznatog HF-a, učestalost je fatalnog i nefatalnog HF-a 10,6 %, šest puta veća nego u za po dobi i spolu sparenih osoba bez HF-a i elektrostimulatora srca.[6]

Čini se da se učestalost smrtnosti od HF-a smanjuje sporije u općoj populaciji nego prethodnih godina.[1] Među bolesnicima s resinkronizacijskom terapijom (CRT) postupno smanjenje iznenadnih srčanih smrti prati se od 2000-ih godina[7] s implikacijom uloge implantabilnih defibrilatora i koncepta sveobuhvatne HF skrbi.

Uočene su znatne regionalne razlike u zbrinjavanju akutnog HF-a, uključujući vrijeme i vrste primijenjenoga liječe-

sodium-glucose cotransporter 2 inhibitors empagliflozin and sotagliflozin in patients with HF were reported: the EMPEROR-Reduced trial in patients with HF with reduced EF with or without type 2 diabetes (T2DM) demonstrated a significant reduction in cardiovascular (CV) death and HF hospitalisations (HFH). In patients with T2DM and HF across the whole EF spectrum after a recent HFH, the SOLOIST trial showed a reduction in the primary endpoint of CV deaths, total HFH, and urgent visits for HF. In addition, in patients with kidney disease with or without diabetes mellitus (DAPA-CKD), dapagliflozin prevented the deterioration of renal function. Two novel drugs, the activator of soluble guanylate cyclase vericiguat and the myosin activator omecamtiv mecarbil, in the large outcome trials VICTORIA and GALACTIC-HF predominantly reduced HFH in high-risk patients with worsening HF. In the AFFIRM-AHF trial, intravenous ferric carboxymaltose reduced HFH in patients with iron deficiency after an HF decompensation.

Year 2020 will be remembered as the year of coronavirus disease of 2019 (COVID-19). The pandemia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a massive impact on global health and economy. When this article is published, >80 million people will have been infected and >1.75 million will have died of the disease. Many others will have died or worsen of their diseases, many with cardiovascular (CV) disease, as an indirect effect of the fear to seek assistance or the collapse of healthcare systems. Yet, advances in science and medical care continued developing during the year. This article reviews important advances in the field of heart failure (HF) presented in 2020.

## Epidemiology

More than 64 million people are living with HF in the world, with an estimated prevalence of 1–2% among adults in developed countries, most often with several comorbidities.[1] The incidence of HF may be stabilizing globally, with decreases in higher-income countries,[2] but increases in lower-income countries, and a shift towards HF with preserved ejection fraction (HFpEF), and increasing due to population ageing and the increase in obesity.[1] Age, traditional risk factors for HF, a sedentary lifestyle, and social deprivation are associated with incident HF.[3] Actually, lifestyle and social determinants of health are attracting more attention in the epidemiology and care of patients with HF.[4] In patients with new-onset HF, the most common first events are cardiac events (36%), recurrent HF (28%), and death (29%).[5]

Non-traditional risk factors, such as pacemaker implantation may play a role in the development of HF: within the first 2 years after implantation in patients without known HF, the incidence of fatal and non-fatal HF is 10.6%, six times higher than for age- and gender-matched individuals without HF and pacemaker.[6]

Mortality rates of HF seem to be declining less rapidly than previously in the general population.[1] Among patients with cardiac resynchronization therapy (CRT), a gradual decrease in sudden cardiac death risk has been observed since the early 2000s[7] with implications for the role of implantable defibrillators and the design of comprehensive HF care models.

Significant regional differences in the management of acute HF have been identified, including timing and types

nja,[8] učestalosti i vremenskih trendova ponovnih prijema.[2,9,10] Ipak, naglašena je važnost razlikovanja između pogoršanja kroničnog od novonastalog oblika HF-a u bolesnika u prvoj hospitalizaciji, jer bolesnici s pogoršanjem/kroničnim HF-om imaju mnogo veće opterećenje komorbiditetima i veći prilagođeni rizik mortaliteta i hospitalizacije zbog HF-a.[10,11]

## Klinička obilježja

### DIJAGNOSTIKA I STRATIFIKACIJA RIZIKA

#### Slikovne metode

Slikovni prikaz ima vodeću ulogu u dijagnozi i stratifikaciji rizika u bolesnika s HF-om. Udruženje za zatajivanje srca Europskoga kardiološkog društva (HFA) u svojim je preporukama nedavno naglasilo središnju ulogu kompletnoga ehokardiografskog pregleda u bolesnika primljenog zbog akutnog zatajivanja srca (AHF).[12] Istraživana je dodatna vrijednost rutinske primjene magnetne rezonancije srca (CMR), kada se bolesnik stabilizira spram same ehokardiografije, kao pomoć pri dijagnozi uzroka HF koja nije povezana s ishemijskom bolesti srca.[13] Selektivna primjena CMR-a, a ne rutinska, više je isplativa za utvrđivanje specifične etiologije HF-a. Važno je reći da bi CMR mogao koristiti pri boljem definiranju fenotipa HFpEF i izbora specifičnog liječenja, kao što bi antagonisti mineralokortikoidnih receptora mogli biti za liječenje bolesnika s HFpEF-om i fibrozom miokarda.[14-17] Dijagnoza HFpEF-a i dalje ostaje izazov, posebice u bolesnika s koegzistirajućim stanjima koja pridonose pojavi zaduhe. Dijastolička disfunkcija, uvećanje lijevog atrija, povećani tlak u lijevom atriju i plućna hipertenzija uobičajeni su u takvih bolesnika.[18,19] Algoritam procjene dijastoličke funkcije iz 2016. preporučen od Europskog udruženja kardiovaskularnih slikovnih metoda (EACVI) pokazao je poboljšanu prognostičku vrijednost u usporedbi s onim iz 2009. godine.[20] Ipak, velik broj nejasno definiranih bolesnika čini kliničke odluke zahtjevnima.[21] Analiza mehanike LA, naprezanja LA i globalnoga longitudinalnog naprezanja (GLS) lijeve klijetke (LV)[22] omogućuje bolju klasifikaciju stupnja dijastoličke disfunkcije i poboljšava individualnu stratifikaciju rizika. Dva algoritma (*H2FPEF* i *ESC HFA-PEFF*) mogu olakšati postavljanje dijagnoze HFpEF-a. Ta dva izračuna imaju jednaku prediktivnu snagu za hospitalizaciju zbog HF-a i smrtni ishod među bolesnicima bez kliničke dijagnoze HF-a.[23] Iako je LVEF ključna za klasifikaciju HF-a, i dalje je riječ o gruboj metodi procjene funkcije LV-a. Intrigantno je da u 17 % bolesnika koji se inicijalno prikažu s očuvanom sistoličkom funkcijom LV-a pokaže kasnije smanjenje LVEF-a na <40 % u šestomjesečnom praćenju, što je povezano s više srčanih incidenata.[24] Parametri mehanizma LV-a (naprezanje LV-a, naprezanje slojeva i rad miokarda) poboljšavaju prognostičke podatke više od LVEF-a.[22,25] Dobrobit liječenja (npr. sakubitril-valsartan, SV) na remodeliranje LV se bolje prikazuje *strainom* LV-a.[26] Mehanizam mehanike miokarda povezan je s disfunkcijom koronarne mikrovaskulature u bolesnika s hipertenzivnim HF-om.[27,28] U AHF-u disfunkcija srčanog simpatikusa, što je ispitivano oslikavanjem s 123 jod-metajodbenzilgvanidinom, povezana je s lošijim ishodima neovisno o vrijednostima LVEF-a.[29]

#### Biomarkeri

Biomarkeri su ključni za dijagnozu i procjenu prognoze u bolesnika s HF-om. Cirkulirajući biomarkeri povezani uz

of treatments used,[8] and rates and time trends of readmission.[2,9,10] However, the importance of distinguishing worsening/chronic HF from new-onset HF in patients with first hospitalization has been highlighted, as patients with worsening/chronic HF have a significantly greater comorbidity burden and higher adjusted risks of mortality and HF readmission.[10,11]

## Clinical aspects

### DIAGNOSTICS AND RISK STRATIFICATION

#### Imaging

Imaging is pivotal in the diagnosis and risk stratification of patients with HF. The European Society of Cardiology (ESC) Heart Failure Association (HFA) has recently highlighted in a position statement the central role of full echocardiographic examination in patients admitted for acute heart failure (AHF).[12] Once the patient is stabilized, the added value of routine cardiac magnetic resonance (CMR) over echocardiography alone to help diagnose the causes of HF not related to ischaemic heart disease has been questioned.[13] Selective rather than routine CMR for identifying specific HF aetiologies is more cost effective. Noteworthy, CMR could serve to better define HFpEF phenotypes and to select patient specific therapies, such as MRA may be for HFpEF patients with myocardial fibrosis.[14-17] The diagnosis of HFpEF remains challenging especially in patients with coexisting conditions that account for dyspnoea. Diastolic dysfunction, left atrial enlargement, elevated left atrial pressure, and pulmonary hypertension are common in these patients.[18,19] The 2016 diastolic dysfunction grading algorithm proposed by the European Association of Cardiovascular Imaging has shown improved prognostic value compared to the 2009 one.[20] However, the high number of patients with doubtful classification renders clinical decision making challenging.[21] The analysis of LA mechanics, LA strain, and left ventricular (LV) global longitudinal strain[22] allows to better classify the degree of diastolic dysfunction and improves individual risk stratification. Two algorithms ($H_2$FPEF and ESC HFA-PEFF) may facilitate HFpEF diagnosis. These two scores have equivalent predictive power of incident HF hospitalization or death among patients without a clinical diagnosis of HF.[23] Although LV ejection fraction (LVEF) is key for HF classification, it remains a crude estimate of LV function. Intriguingly, 17% of patients with initially preserved LV systolic function show a decrease in LVEF below 40% at 6 months follow-up, which is associated with more cardiac events.[24] Parameters of LV mechanics (LV strain, multilayer strain and myocardial work) provide incremental prognostic information over LVEF.[22,25] The benefit of treatment [i.e. sacubitril/valsartan (SV)] on LV remodelling is also better captured by LV strain.[26] Myocardial mechanics is linked to coronary microvascular dysfunction in patients with hypertensive HF.[27,28] In AHF, cardiac sympathetic nerve dysfunction, as evaluated by $^{123}$I-metaiodobenzylguanidine imaging, is associated with poor outcome irrespective of LVEF.[29]

#### Biomarkers

Biomarkers are key for diagnosis and prognostic evaluation in patients with HF. Circulating biomarkers related to extracellular matrix regulation were abnormal in patients with HFpEF, displayed prognostic value, and were influenced favourably

regulaciju ekstracelularnog matriksa koji su povišeni u bolesnika s HFpEF-om, pokazali su prognostičku vrijednost te je primjena SV-a imala povoljan učinak na njih u studiji *PARAGON-HF*.[30] U HF-u sa sniženom LVEF (HFrEF), apsolutne vrijednosti NT-proBNP, hsTnT i sST2 predviđale su ishode neovisno o dobi, spolu i kategoriji LVEF-a.[31] Objavljene su razlike u razinama cirkulirajućih biomarkera vezano za starenje bolesnika s HF-om, uz povećanje razine proteina vezanih uz organizaciju ekstracelularnog matriksa, upalnih procesa, regulacije tumorskih stanica i slabije ekspresije funkcija tumorske proliferacije.[32]

U AHF-u poseban je izazov utvrđivanje infekcije kao „okidača". Prokalcitonin (PCT) se pojavio kao alternativa CRP-u za potvrdu bakterijskih infekcija. U novim multicentričnim istraživanjima otvorenog dizajna, strategija PCT-om vođenim započinjanjem antibiotske terapije bila je efikasnija od standardne skrbi u poboljšanju kliničkih ishoda.[33] Omics fenotipizacija vjerojatna je sljedeća granica prema razumijevanju mehanizma bolesti i heterogenosti.[34] U nedavnom primjeru uključivanjem panela od triju biomarkera metabolita u procjenu rizika poboljšala se prognostička korist od NT-proBNP-a pri predviđanju dugoročne CV smrtnosti.[35]

## ZATAJIVANJE SRCA U VRIJEME PANDEMIJE COVID-A 19

Uloga receptora angiotenzin-kovertirajućeg enzima 2 (ACE) kod infekcije ljudskih stanica SARS-CoV-2 i u patofiziologiji COVID-a 19,[36] i loša prognoza kardioloških bolesnika s COVID-om 19[37] potaknuli su zabrinutost o potencijalnom štetnom učinku liječenja ACE inhibitorima i blokatorima angiotenzinskih receptora (ARB). Spomenuti lijekovi mogu ili smanjiti akutno oštećenje pluća preveniranjem angiotenzin-II posredovane upale pluća ili povećati SARS-CoV-2 plućno oštećenje *up*-regulacijom ACE2 receptora.[38,39] Opservacijske studije odbacile su hipotezu o štetnom učinku ACEI/ARB-a.[40-43] Studija *BRACE CORONA* nije utvrdila lošije ishode u bolesnika s COVID-om 19 randomiziranih u nastavak ili prekid njihova kroničnog liječenja ACEI/ARB-om (prikazana na ESC kongresu, još neobjavljeno). Učestalost AHF-a ili dekompenzacija kroničnog HF-a među bolesnicima s COVID-om 19 je visoka i s lošom prognozom.[44] U posredne učinke pandemije ubraja se smanjenje hospitalizacija zbog HF-a tijekom lokalnih izbijanja epidemije[45-47] i porast bolničke smrtnosti,[45,47], što je velik izazov za liječenje i praćenje bolesnika s HF-om te provođenje kliničkih istraživanja. Objavljene su preporuke za prevladavanje tih izazova.[48-50]

## SPOL I ZATAJIVANJE SRCA

Žene čine polovicu bolesnika s HF-om. U njih je registrirana snižena učestalost HF-a do dobi od 75 godina i veći udio HFpEF-a, što je vjerojatno povezano s većom prevalencijom pretilosti i šećerne bolesti.[1] Žene s HF-om imaju više simptoma i lošiju kvalitetu života u usporedbi s muškarcima.[51] Značajna razlika vezana za spol opisana je u Europi u liječenju akutnog i kroničnog HF-a[8,52], uključujući manju primjenu liječenja prema smjernicama – što je uglavnom objašnjeno starijom dobi i komorbiditetima više nego samim spolom – uz nižu stopu smrtnosti i hospitalizacija zbog HF-a u žena. Nepostojanje razlika vezanih uz spol za kliničke učinke terapije HF-a[53,54] ne opravdava ove razlike, iako postoji mogućnost da žene s HF-om mogu imati dobrobit od liječenja do viših razina LVEF-a nego što se prije mislilo.[54] Drukčiji pogled na razliku prema

by SV in PARAGON-HF.[30] In HF with reduced LVEF (HFrEF), absolute NT-proBNP, hs-TnT, and sST2 levels predict outcomes independent of age, sex, and LVEF category.[31] Differential circulating levels of biomarkers associated with ageing in patients with HF have been reported, with increasing levels of proteins associated with extracellular matrix organization, inflammatory processes, and tumour cell regulation and lower expression of tumour proliferation functions.[32]

In AHF, a specific challenge is to identify infection as a trigger of AHF. Procalcitonin (PCT) has emerged as an alternative for C-reactive protein in diagnosing bacterial infection. In a recent randomized, multicentre, open study, a strategy of PCT-guided initiation of antibiotic therapy was more effective than standard care in improving clinical outcomes.[33] Omics phenotyping is likely the next frontier to unravel disease mechanisms and heterogeneity.[34] As a recent example, incorporating a panel of three metabolite-based biomarkers into a risk score improved the prognostic utility of NT-proBNP by predicting long-term CV death.[35]

## HEART FAILURE DURING THE COVID-19 PANDEMIC

The role of the angiotensin-converting enzyme (ACE) receptor 2 in the infection of human cells by SARS-CoV-2 and in the pathophysiology of COVID-19,[36] and the poor prognosis of cardiac patients with COVID-19[37] raised the concern of a potential deleterious effect of the treatment with ACE inhibitors and angiotensin receptor blockers (ARB). These drugs may either decrease acute lung damage, prevent angiotensin-II-mediated pulmonary inflammation or increase the SARS-CoV-2 pulmonary damage by the up-regulation of ACE2 receptors.[38,39] Observational studies refuted the hypothesis of a deleterious effect of ACEI/ARB.[40-43] The BRACE CORONA trial found no worse outcomes in patients with COVID-19 allocated to continuation or interruption of their chronic ACEI/ARB treatment (presented at the ESC Congress, data not published). The incidence of AHF or decompensation of chronic HF among patients with Covid-19 is high and with poor prognosis.[44] Indirect effects of the pandemic included the reduction in HF hospitalizations during local outbreaks[45-47] with increases in their hospital mortality,[45,47] and major challenges for the management and Follow-up of HF patients, and the conduct of clinical trials. Recommendations to overcome these challenges have been released.[48-50]

## SEX AND HEART FAILURE

Women account for half of patients with HF with a lower incidence rate until the age of 75 years, a higher proportion of HFpEF, probably related to the higher prevalence of obesity and diabetes mellitus.[1] Women with HF present a greater symptom burden and poorer quality of life as compared with men.[51] Significant sex-related differences have been described in Europe in the management of acute and chronic HF[8,52] including a lower use of guideline-directed medical therapies—which seem to be mostly explained by older age and comorbidity rather than by sex itself—with lower crude rates of death and HF hospitalization in women. The lack of sex-related differences in the clinical effect of HF therapies[53,54] does not justify these differences, although the possibility has been suggested that women with HF might benefit from treatment to a higher level of LVEF than previously considered.[54] A different perspective of the gender gap

spolu kod HF-a jest manji udio ženskih autora u HF praktičnim smjernicama i studijama, u rasponu između 11 % i 24%, sa skromnim povećanjem tijekom vremena u referencama europskih i američkih smjernica, ali ne i u HF studijama. Važno je reći da su HF studije sa ženama prvim ili starijim autorima povezane s većim postotkom uključenih žena sudionica.[55]

### KOMORBIDITETI

Komorbiditeti su bitni jer utječu na kliničku sliku, liječenje i ishode bolesnika s HF-om. Opterećenje je komorbiditetima veće u starijih bolesnika, u žena i u onih s HFpEF-om[56-58], što se često zanemaruje.[59] Posebice važna stanja u bolesnika s HF-om uključuju fibrilaciju atrija,[60] koja ima kompleksan odnos s HF-om i zahtijeva više istraživanja.[61,62] Jedan takav primjer jest izostanak povećanja rizika od smrtnosti povezanog s porastom frekvencije srca u bolesnika s HFrEF-om i fibrilacijom atrija kad se uspoređuju sa sinusnim ritmom.[60,63] Bubrežna je bolest još jedno takvo stanje, pri kojemu se bubrežna funkcija mijenja tijekom razvoja bolesti ili kao odgovor na liječenje HF-a. Klinički odgovori, uključujući pogoršanje bubrežne funkcije i pseudopogoršanje bubrežne funkcije, i njihovi patofiziološki kolerati, tj. funkcija tubula (odgovor na diuretike) povrh procijenjene glomerularne filtracije (eGFR), trebaju se razumjeti kako bi bili pravilno liječeni, prilagođujući terapiju izmijenjenoj situaciji.[64,65]

## Specifične situacije

### AKUTNO ZATAJIVANJE SRCA

U bolesnika s akutnim HFrEF-om, isaroxime, inhibitor sarkolemalne Na+/K+ pumpe aktivacijom SERCA2a pumpe, poboljšao je funkciju srca bez velikih nepovoljnih učinaka u maloj mehanicističkoj studiji.[66] Cimlanod, nitroxyl donor primijenjen infuzijom tijekom 48 sati, bio je bio prilično dobro podnošen u manjim dozama, dok su veće doze uzrokovale neprihvatljivu hipotenziju. Nastupilo je znatno poboljšanje vrijednosti NT-proBNP-a, ali ne i zaduhe (prikazano na HFA Discoveries, nije objavljeno). Niz preporuka stručnih društava rezimiralo je ulogu slikovnih metoda[12] ili liječenja AHF-a u specifičnim situacijama, kao što su akutni koronarni sindrom[67] ili fibrilacija atrija.[68]

### KARDIOGENI ŠOK

Istodobno, iako se čini da je incidencija kardiogenog šoka u padu, to stanje i dalje nosi veliki rizik od smrtnosti.[69] Ove su godine objavljeni nova klinička klasifikacija kardiogenog šoka[70] i dva mišljenja stručnih društava.[71,72] Studija *SWEdish evaluation of left Ventricular Assist Device* (SweVAD) istražit će utjecaj mehaničke cirkulatorne potpore spram smjernica vođene medikamentne terapije na preživljavanje u bolesnika s AHF-om nepodobnih za transplantaciju srca.[73]

### PERIPARTALNA KARDIOMIOPATIJA

Peripartalna kardiomiopatija (PPCM) prvi je uzrok HF-a u žena za vrijeme / nakon trudnoće.[74-76] U Registar ESC EORP uključeno je >700 žena s PPCM-om iz 49 zemalja. Pokazalo se da PPCM pogađa žene iz bilo koje regije ili etničke pripadnosti. Unutar 6 mjeseci nakon postavljanja dijagnoze prosječne učestalosti smrtnosti majke, ponovne hospitalizacije i neonatalne smrtnosti iznosila su 6 %, 10 % i 5 % uz registrirane značajne regionalne razlike. Do oporavaka LVEF-a došlo je kod 46 % žena.[77] Liječenje takvih bolesnica prikazano je u nedavno objavljenom članku.[78]

in HF is the lower proportion of female authors in HF practice guidelines and trials, ranging between 11% and 24% only, with modest increases over time in European and US guidelines references but not in HF trials. Importantly, HF trials with a woman first or senior author are associated with a higher proportion of enrolled female participants.[55]

### COMORBIDITIES

Comorbidities are important because they impact the clinical presentation, management, and outcomes of HF patients. The burden of comorbidities is higher in older patients, women and those with HFpEF,[56-58] which are often ignored.[59] Particularly relevant conditions in HF patients include atrial fibrillation,[60] which has complex interrelations with HF needing more research.[61,62] One example is the lack of increase in mortality risk associated with elevated heart rate in patients with HFrEF and atrial fibrillation, as compared to sinus rhythm.[60,63] Renal disease is one other, with renal function often changing during the course of the disease or as a response to HF therapies. Clinical responses, including worsening renal function and pseudo-worsening renal function, and their pathophysiological correlates, i.e. tubular function (diuretic response) beyond estimated glomerular filtration rate (eGFR), need to be understood to be properly managed, adapting therapies to the changing situation.[64,65]

## Specific situations

### ACUTE HEART FAILURE

In patients with acute HFrEF, istaroxime, an inhibitor of the sarcolemmal $Na^+/K^+$ pump activating the SERCA2a pump, improved cardiac function without major adverse effects in a small mechanistic trial.[66] Cimlanod, a nitroxyl donor infused over 48 h, was reasonably well tolerated at a lower dose whereas higher doses caused unacceptable hypotension. There was improvement of NT-ProBNP but not on dyspnoea (presented at HFA Discoveries, data not published). A number of position papers have summarized the role of imaging[12] or the management of AHF in specific situations, such as acute coronary syndromes[67] or atrial fibrillation.[68]

### CARDIOGENIC SHOCK

While its incidence seems to be decreasing, cardiogenic shock still conveys a high mortality risk.[69] A new clinical classification,[70] and two position papers[71,72] on cardiogenic shock have been published this year. The SWEdish evaluation of left Ventricular Assist Device (SweVAD) will examine the impact of mechanical circulatory support vs. guideline-directed medical therapy on survival in a population of AHF patients ineligible for heart transplant.[73]

### PERIPARTUM CARDIOMYOPATHY

Peripartum cardiomyopathy (PPCM) is the first cause of HF in women during/after pregnancy[74-76] The ESC EORP registry on PPCM enrolled >700 women with this condition from 49 countries. It showed that PPCM affects women from any region or ethnicity. Within 6 months after diagnosis, the average rates of maternal mortality, readmission, and neonatal mortality were, respectively, 6%, 10%, and 5%, with marked regional variations. Recovery of LVEF occurred in 46% of women.[77] The management of these patients is reviewed in a recent paper.[78]

### ZATAJIVANJE SRCA S OPORAVLJENOM EJEKCIJSKOM FRAKCIJOM LIJEVE KLIJETKE

Ove je godine predložena radna definicija HF-a s oporavljenom ejekcijskom funkcijom lijeve klijetke (HFrecEF). Ona uključuje potvrdu smanjene (<40 %) LVEF na početku, apsolutno poboljšanje LVEF-a za >10 % i drugo mjerenje koje je pokazalo >40 %.[79] Obrat remodeliranja LV-a povezan je s poboljšanom kontraktilnošću miocita i šupljine LV-a te boljim kliničkim ishodima. Međutim, u znatnog se udjela bolesnika s HFrecEF-om ponovno razvije disfunkcija LV-a i HF-a. Usprkos oporavku strukturnih i funkcionalnih oštećenja, mnoge molekularne promjene koje su nastale na više razina tijekom LV remodeliranja ostaju disregulirane. Stoga se smjernicama vođena medikamentna terapija i terapija uređajima za bolesnike s HFrecEF-om treba nastaviti neodređeno uz učestalo kliničko praćenje.[79]

### ZATAJIVANJE SRCA U BOLESNIKA S KARCINOMOM

Uloga CV slikovnih metoda u bolesnika s karcinomom koji primaju kardiotoksičnu terapiju istaknuta je u preporukama HFA[12] i smjernicama Europskog društva za medicinsku onkologiju.[80] Uloga fokusne ehokardiografije[81] i CMR-a[82] također je bila nedavno publicirana. U svakodnevnoj je praksi potrebno biti pažljiv pri uporabi metode kasnog nakupljanja gadolinija ili kvalitativnog T2 slikovnog STIR prikaza za isključenje miokarditisa izazvanog *checkpoint* inhibitorima.[83] Slikovne su metode temelj praćenja kardiotoksičnosti i utvrđivanja suptilnih pogoršanja funkcija miokarda koje se pojavljuju prije prelaska tradicionalnog praga sistoličke disfunkcije LV-a (LVEF <50 %).[84,85]

### DISFUNKCIJA DESNE KLIJETKE

Disfunkcija desne klijetke (RV) i desnog atrija pridonosi HFpEF-u. Isto tako, disfunkcija RV-a (smanjena sistolička brzina RV-a i promjena njegove frakcijske areje) i oštećenje sprege RV – plućna arterija češće se utvrde u bolesnika s HFpEF-om u kojih se pri naporu razvija plućna kongestija.[86] Aktivacija endotelin i adrenomedulin neurohormonalnih puteva povezana je s plućnim hemodinamskim poremećajima, smanjenom frakcijskom rezervom RV-a, smanjenim udarnim volumenom srca i većim smanjenjem vršnog $VO_2$ u bolesnika s HFpEF-om.[87] Najčešći uzroci disfunkcije desne klijetke (RVD) jesu bolesti lijeve strane srca (46 %), plućna tromboembolijska bolest (18 %), kronična plućna bolest/hipoksija (17 %) i plućna arterijska hipertenzija (11 %). Prosječna je jednogodišnja smrtnost u bolesnika s RVD-om je velika (>40 %), najveća među bolesnicima s kroničnom plućnom bolesti.[88] Prisutnost RVD-a i implantacija CRT-a predviđaju pogoršanje remodelinga LV-a i preživljenja.[89]

## Farmakoterapija

### ANGIOTENZIN RECEPTOR-NEPRILISIN INHIBITORI (STUDIJE *PARAGON, PARADIGM, PARALLAX*)

Angiotenzin receptor-neprilisin inhibitori (ARNI) u subanalizi studije *PARADIGMN-HF* pokazuje smanjenje rizika od iznenadne srčane smrti, neovisno o uporabi implantabilnih srčanih defibrilatora.[90] Smanjenje volumena klijetki i povećanje LVEF-a nađeno je pri standardnoj ehokardiografiji u bolesnika

### HF WITH RECOVERED LEFT VENTRICULAR EJECTION FRACTION

This year, a working definition of HF with recovered left ventricular ejection fraction (HFrecEF) has been proposed. This includes: (i) documentation of a decreased LVEF < 40% at baseline; (ii) ≥10% absolute improvement in LVEF; and (iii) a second measurement of LVEF >40%.[79] Reverse LV remodelling is associated with improved myocyte and LV chamber contractility and better clinical outcomes. However, a significant proportion of patients with HFrecEF develop recurrences of LV dysfunction and HF. Despite improvements in structural and functional abnormalities, many of the multilevel molecular changes occurring during LV remodelling remain dysregulated in reverse remodelled hearts. Therefore, guideline-directed medical and device therapy for patients with HFrecEF should be continued indefinitely with close clinical follow-up.[79]

### HF IN CANCER PATIENTS

The role of CV imaging in cancer patients receiving cardiotoxic therapies has been highlighted in a position statement by the HFA[12] and in the European Society for Medical Oncology guidelines.[80] The role of focus echocardiography[81] and CMR[82] has also been recently discussed. In daily practice, caution should, however, be given if using late gadolinium enhancement or qualitative T2-weighted STIR imaging-only approach for the exclusion of checkpoint inhibitor-associated myocarditis.[83] Imaging is cornerstone for monitoring cardiotoxicity and identifying subtle impairment of myocardial function occurring prior crossing the traditionally defined threshold of LV systolic dysfunction (LVEF < 50%).[84,85]

### RIGHT VENTRICULAR DYSFUNCTION (RVD)

RV and right atrium dysfunction contribute to HFpEF pathophysiology. Also, RV dysfunction (lower RV systolic velocity and RV fractional area change) and impairment in RV-pulmonary artery coupling are more frequently found in HFpEF patients developing acute lung congestion with exercise.[86] Activation of the endothelin and adrenomedullin neurohormonal pathways is associated with pulmonary haemodynamic derangements, reduced RV functional reserve, reduced cardiac output, and more severe impairment of peak VO2 in HFpEF patients.[87] The most common causes of RVD are left-sided heart diseases (46%), pulmonary thromboembolic disease (18%), chronic lung disease/hypoxia (17%), and pulmonary arterial hypertension (11%). Average 1-year mortality in patients with RVD is high (>40%), highest among chronic lung disease patients.[88] The presence of RVD at CRT implantation predicts worsening LV remodelling and survival.[89]

## Pharmacotherapies

### ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITORS (PARAGON, PARADIGM, PARALLAX)

Angiotensin receptor–neprilysin inhibitor (ARNI) showed, in a sub-analysis of PARADIGM-HF, a reduction in sudden cardiac death risk regardless of the use of implantable cardiac defibrillators.[90] Reduction in ventricular volumes and increase in LVEF have been observed with standard echocardiography in patients after 6 months on SV, but improvement in global longitudinal strain is apparent after 3 months.[26] In

nakon 6 mjeseci liječenja primjenom SV-a, dok se poboljšanje longitudinalnog naprezanja pojavljuje nakon 3 mjeseca.[26] U maloj skupini bolesnika u terminalnoj fazi bubrežne bolesti primjena SV-a pokazala se učinkovitom i sigurnom.[91] Istraživanje *LIFE* u kojemu se uspoređuje SV s valsartanom u NYHA IV. stadiju bolesnika s HFrEF-om, premda je prije vremena prekinuta zbog pandemije COVID-a 19, donosi informacije o liječenju ARNI-jem u bolesnika s uznapredovalim HF-om.[92]

Istraživanje *PARALLAX* testiralo je učinkovitost SV-a u usporedbi s optimalnom temeljnom terapijom u bolesnika s HFpEF-om. Utvrđeno je snizivanje vrijednosti NT-proBNP-a (do 12 tjedana od početne vrijednosti), no nije bilo učinka na 6-minutnu hodnu prugu (do 24 tjedna od početnog testiranja); spomenut je prikazan na kongresu ESC 2020. – podatci nisu publicirani. U studiji *PARAGON* u bolesnika s HFpEF-om primjena SV-a nije rezultirala nižom učestalošću hospitalizacija zbog HF-a i smrću. Od 12 prespecificiranih subgrupnih analiza, čini se da spol i LVEF modificiraju učinak SV-a spram valsartana, u usporedbi s primarnim zajedničkim ishodom. Premda nije uočen pozitivan ishod u muškaraca, nađeno je znatno smanjenje hospitalizacija u žena.[93] Isto tako, čini se da bolesnici imaju više dobrobiti od SV-a ako se s liječenjem započinje ranije tijekom hospitalizacije.[94] Temeljni i srednji sistolički tlak od 120 do 129 mmHg identificiran je kao najmanje rizičan u bolesnika s HFpEF-om, no djelovanje SV-a na smanjenje tlaka ne utječe na njegov konačni učinak na ishod, neovisno o spolu.[95] U usporedbi s valsartanom, SV smanjuje rizik od učinaka na bubreg i usporuje pad u stupnju procijenjene glomerularne filtarcije.[96] Smanjenje razine mokraćne kiseline također je povezano s poboljšanim ishodom.[97] Metaanaliza učinkovitosti različitih antagonista RAAS-a u kliničkim istraživanjima koja su provođena na bolesnicima s HFpEF-om (*PEP-CHF, CHARM-preserved, I-PRESERVE, TOPCAT, PARAGOM-HF*) pokazuje da nema statistički značajne razlike u ukupnom ili CV mortalitetu pri liječenju antagonistima RAAS-a i placebom, no utvrđeno je signifikantno smanjenje rizika od hospitalizacija zbog HF-a u skupini liječenoj ARNI-jem, u usporedbi s kontrolnom skupinom (OR, 0,73; 95 % CI, 0,61 – 0,87) i skupinom bolesnika na ARB (OR, 0,80; 95 % CI, 0,71 – 0,91).[98]

Analiza podataka bolesnika iz studija *PARADIGM-HF* i *PARAGON-HF* (SV prema enalaprilu kod HFrEF-a te SV prema valsartanu kod HFpEF-a), kao i studije *CHRAM-Alternativa* i *CHARM-Preserved* (kandesartan prema placebu) pokazuje da primjena SV-a u usporedbi s inhibitorima RAAS-a poboljšava ishode kroz različite razine LVEF-a, uz smanjenje rizika (RR) od 0,54 (95 % CI, 0,45 – 0,65) za ponavljani zajednički ciljni ishod u usporedbi s placebom (P<0.001). Povoljni ishodi liječenja bili su značajni u bolesnika s LVEF-om <60 %, ali ne i u onih s LVEF-om >60 %.[99] Rezultati su bili usporedivi s prethodnom *post hoc* analizom iz studije *TOPCAT* i studija s beta-blokatorima, što pokazuje da je granična razina LVEF-a za povoljni ishod liječenja bila oko 55 %. Analize pokazuju da u studijskoj populaciji s LVEF-om od 40 do 55% mogu biti uspješni različiti načini liječenja HF-a (**slika 1**).[100]

## NATRIJ-GLUKOZA KOTRANSPORTER 2 INHIBITORI (ISTRAŽIVANJA *EMPEROR-REDUCED, DAPA-HF, SOLOIST, VERTIS, SUGAR-DM-HF, EMPA-TROPISM [ATRU-4]*)

U bolesnika s dijabetesom tipa 2 empagliflozin i dapagliflozin, lijekovi iz skupine natrij-glukoza kotransporter 2 (SGLT-2) a small cohort of patients with end stage renal disease, SV showed efficacy and safety.[91] The LIFE Trial, comparing SV to valsartan in NYHA Class IV HFREF patients, although prematurely interrupted because of the COVID 19 pandemia, will still provide information about ARNI as a treatment option for advanced HF patients.[92]

The PARALLAX trial tested the efficacy of SV vs. optimal individualised background therapy in HFpEF patients and found a reduction in NT-proBNP from baseline to 12 weeks but no effect on six-minute walk distance from baseline to 24 weeks (presented at ESC 2020—data not published). In the PARAGON Trial in patients with HFpEF, SV did not result in a lower rate of total hospitalizations for HF and death. Of the 12 pre-specified subgroup analyses, sex and LVEF appeared to modify the effect of SV vs. valsartan on the primary composite outcome. Although no benefit was apparent in men, there was a significant reduction in HF hospitalizations in women.[93] Also, patients seemed to derive more benefit from SV when started early after hospitalization.[94] Baseline and mean achieved systolic blood pressure of 120–129 mm Hg identified the lowest risk HFpEF patients, but the blood pressure-lowering effects of SV did not account for its effects on outcomes, regardless of sex.[95] Compared with valsartan, SV reduced the risk of renal events and slowed the decline in estimated glomerular filtration rate.[96] Reduction in serum uric acid was also associated with improved outcomes.[97] A meta-analysis assessing the efficacy of different renin–angiotensin–aldosterone system (RAAS) antagonists in clinical trials performed in HFpEF patients (PEP-CHF, CHARM-preserved, I-PRESERVE, TOPCAT, PARAGON-HF) showed no statistical difference in all-cause and CV mortality among RAAS antagonists and placebo, but a significantly decreased risk in HF hospitalizations in patients allocated to receive ARNI compared with controls (OR, 0.73, 95% CI, 0.61–0.87) and ARB (OR 0.80, 95% CI, 0.71–0.91).[98]

A patient-level data analysis from the PARADIGM-HF and PARAGON-HF trials (SV vs. enalapril in HFrEF and SV vs. valsartan in HFpEF, respectively), and the CHARM-Alternative and CHARM-Preserved trials (candesartan vs. placebo) showed that, compared with RAAS inhibitors, SV improved outcomes across the range of LVEF, with a risk reduction (RR) of 0.54 [95% confidence interval (CI) 0.45–0.65] for the recurrent primary endpoint compared with putative placebo ($P < 0.001$). Treatment benefits were robust in patients with LVEF < 60%, but not in those with LVEF > 60%.[99] These results are in line with prior *post hoc* analyses from the TOPCAT study and β-blocker trials suggesting that the cut-off of LVEF for a beneficial treatment effects is 55%. These analyses show that in the sparsely studied population of patients with an LVEF of 40–55%, several HF treatments might provide benefit (**Figure 1**).[100]

## SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS (EMPEROR-REDUCED, DAPA-HF, SOLOIST, VERTIS, SUGAR-DM-HF, EMPA-TROPISM [ATRU-4])

In patients with type 2 diabetes, the sodium-glucose cotransporter 2 (SGLT-2) inhibitors empagliflozin and dapagliflozin reduce the risk of HF hospitalization regardless of baseline CV risk or history of HF.[101,102] In The VERTIS trial, ertugliflozin did neither significantly reduce CV events, nor the combined

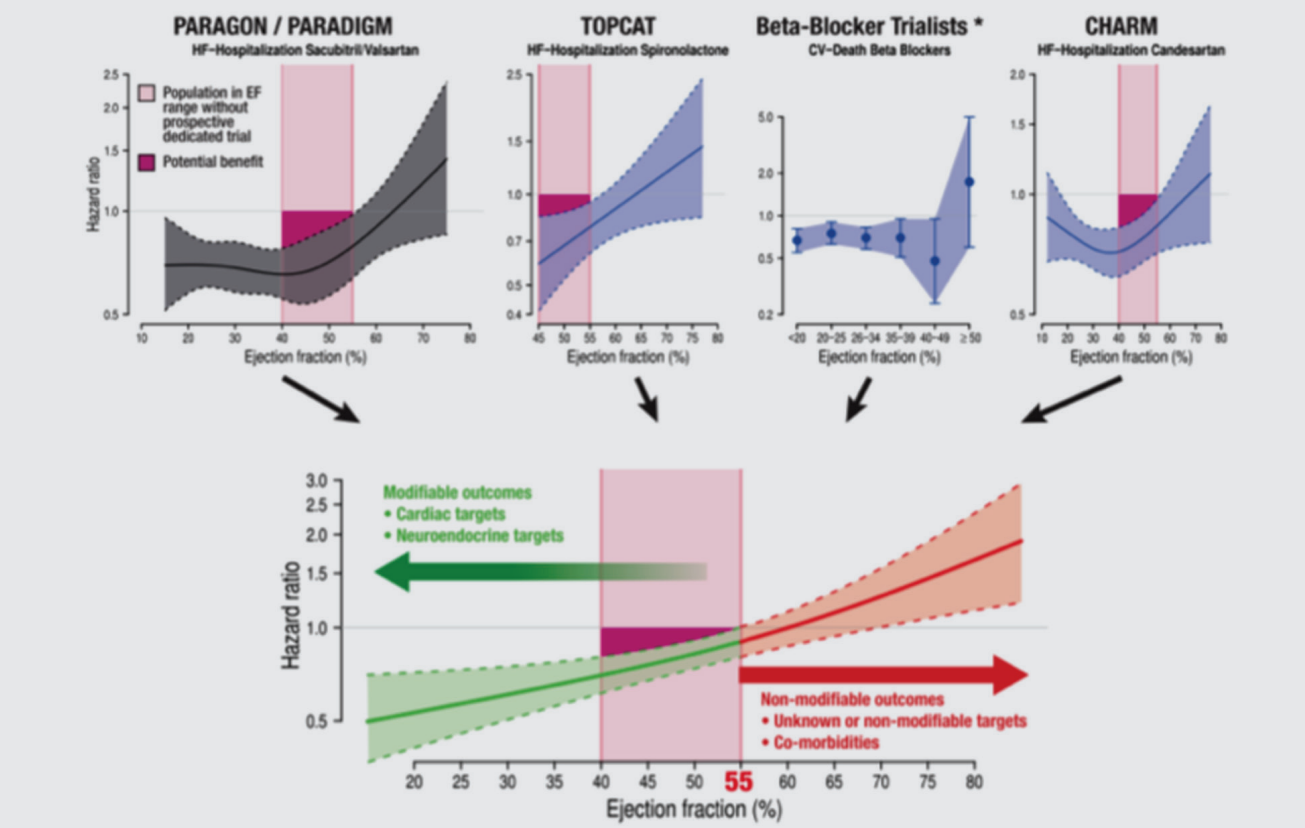


**FIGURE 1. Results from different trials testing a number of drugs commonly used to treat heart failure, pointing to an extended benefit up to a left ventricular ejection fraction of 55%. For patients with left ventricular ejection fraction >55%, a population group usually presenting several comorbidities, there is still no evidence of a drug improving prognosis. Reprinted from Böhm et al.[100]**

(from Bueno H, Moura B, Lancellotti P, Bauersachs J. The year in cardiovascular medicine 2020: heart failure and cardiomyopathies. Eur Heart J. 2021 Feb 11;42(6):657-670. https://doi.org/10.1093/eurheartj/ehaa1061, by permission of OUP on behalf of the ESC)

inhibitora, smanjuju rizik od hospitalizacija zbog HF-a neovisno o početnom CV riziku ili anamnestičkim podatcima o HF-u.[101,102] U studiji *VERITAS* primjena ertugliflozina nije znatno smanjila CV događaje ni zajednički ishod (CV smrtnost i hospitalizacije zbog HF-a)[103], no smanjena je učestalost hospitalizacija zbog HF-a.[104]

Studija *DAPA-HF* u bolesnika s HFrEF-om je pokazala signifikantno smanjenje CV smrtnosti i događaja vezanih za HF.[105,106] Ovaj značajni učinak bio je analiziran u nekoliko istraživanja koja su objavljena tijekom 2020. Povoljno djelovanje dapagliflozina nije ovisilo o tome ima li bolesnik dijabetes ili nema, a pojavljivalo se pri svim vrijednostima HbA1C[107], kao i neovisno o temeljnoj bubrežnoj funkciji, arterijskom tlaku, životnoj dobi ili terapiji HF-a.[108-111] Dapagliflozin poboljšava simptome, tjelesnu kondiciju i kvalitetu života[112] i pokazuje da je troškovno učinkovit u liječenju HFrEF-a u zdravstvenim sustavima Velike Britanije, Njemačke i Španjolske.[113] Dapagliflozin također snizuje stupanj sniženja bubrežne funkcije u bolesnika s HFrEF-om[111], kao i u onih s kroničnom bubrežnom bolesti (CKD), u skladu s rezultatima studije *DAPA-CKD* u kojoj je također uočeno da liječenje tim lijekom smanjuje rizik od pogoršanja renalne funkcije, terminalnoga stadija bubrežne bolesti ili smrtnog ishoda.[111] Protektivni je učinak registriran u bolesnika neovisno o prisutnosti dijabetesa.[111,114]

endpoint of CV death/HF hospitalization[103] but reduced HF hospitalizations.[104]

In patients with HFrEF, DAPA-HF has demonstrated a significant reduction in CV mortality and HF events.[105,106] This robust effect was analysed in more detail in several seminal papers published in 2020. The benefit of dapagliflozin was independent of the diabetes status, occurring across all levels of HbA1C,[107] as well as of baseline renal function or blood pressure, patient age, or background HF therapy.[108–111] Dapagliflozin improved symptoms, physical function, and quality of life[112] and was shown to be a cost-effective treatment for HFrEF in the UK, German, and Spanish healthcare systems.[113] Dapagliflozin also reduces the rate of decline in renal function in HFrEF patients.[111] as well as in patients with chronic kidney disease, as shown in the DAPA-CKD trial, where treatment with dapagliflozin reduced the risk of worsening renal function, end-stage kidney disease, or death. [111] This protective effect was observed in patients with or without diabetes.[111,114]

Empagliflozin also showed marked beneficial effects in HFrEF patients independently from diabetes status, with a significant reduction in the primary composite endpoint of CV death and HF events (hazard ratio (HR), 0.75; 95% CI, 0.65–

Empagliflozin također pokazuje značajan povoljni učinak u bolesnika s HFrEF-om neovisno o dijabetesu, sa znatnim smanjenjem u primarnome zajedničkom ishodu od CV smrtnosti i događaja vezanih s HF-om (*hazard ratio* – HR 0,75; 95 % CI, 0,65 – 0,86; P<0,001), sekundarnom ishodu – ukupnim hospitalizacijama zbog HFa (HR, 0,70; 95 % CI, 0,58 – 0,85; P<0,001), godišnjem padu u eGFR (–0,55 vs. –2,28 mL/min/1,73 $m^2$ od površine tijela po godini; P<0,001), riziku od ozbiljnih renalnih ishoda[115], riziku i ukupnom broju bolničkih i ambulantnih pogoršanja HF-a, što je registrirano rano nakon početka liječenja i održava se trajanjem liječenja.[116] Povoljni se učinak također bilježi u manjem opsegu i u bolesnika koji su već prije liječeni ARNI-jem[117], neovisno o prisutnosti dijabetesa i vrijednostima HbA1c,[118] u onih s kroničnom bolešću bubrega i bez nje i neovisno o težini temeljnog oštećenja bubrega.[119]

U studiji *SUGAR-DM-HF* emfagliflozin snizuje volumene lijeve klijetke mjereno magnetnom rezonancijom u bolesnika s HFrEF-om i tipom 2 dijabetesa ili preddijabetesa.[120] Mehanistička studija *EMPA-TROPISM (ATRU-4)* pokazuje povoljan učinak emfagliflozina u poboljšanju volumena i mase lijeve klijetke, sistoličke funkcije lijeve klijetke, funkcionalnog kapaciteta i kvalitete života, u bolesnika s HFrEF-om bez dijabetesa.[121] Ako se zbroje svi dokazi, može se utvrditi da SGLT-2 inhibitori snizuju ukupnu i CV smrtnost, poboljšavaju bubrežnu funkciju u bolesnika s HFrEF-om, podržavajući ulogu dapagliflozina i empagliflozina u smislu standardne skrbi za bolesnike s HFrEF-om.[119,122]

Sotagliflozin je SGLT-2 inhibitor koji također pokazuje gastrointestinalnu SGLT-1 inhibiciju i time smanjuje intestinalnu apsorpciju glukoze. Proučavan je u bolesnika s tipom 2 dijabetesa nakon nedavne hospitalizacije zbog pogoršanja HF-a (*SOLOIST-WHF*). Bolesnici su uključeni neovisno o LVEF-u, a 78 % njih imalo je LVEF <50 %. Primarni zajednički cilj (CV smrtnost, ukupni broj hospitalizacija i hitan pregled zbog HF-a) bio je signifikantno snižen u onih liječenih sotagliflozinom (HR, 0,67; 95 % CI, 0,52 – 0,85; P< 0,001). Rezultati su konzistentni među subgrupama, a posebno u osoba s LVEF-om >50 %.[123] Sotagliflozin je također proučavan u bolesnika s tipom 2 dijabetesa, kroničnom bolešću bubrega i povećanim CV rizikom (*SCORED*).[124] Primarni zajednički ishod (CV smrtnost, ukupne hospitalizacije i hitni pregledi zbog HF-a) bio je znatno snižen u onih liječenih sotagliflozinom (HR, 0,67; 95 % CI, 0,52 – 0,85; P <0,001). Nužno je napomenuti da su obje studije sa sotagliflozinom prekinute ranije nego što je bilo planirano zbog prekida financiranja od sponzora.

## AKTIVATOR SOLUBILNE GUANILAT CIKLAZE (STUDIJE *VICTORIA, VITALITY, CAPACITY*)

Aktivator solubilne guanilat ciklaze (sGC) vericiguat istraživan je u studiji *VICTORIA* na 5050 bolesnika s nedavnom dekompenziranom fazom kroničnog HF i LVEF <45%.[125,126] Vericiguat znatno smanjuje primarni ishod od CV smrti ili prve hospitalizacije zbog HF-a (HR, 0,90; 95 % CI, 0,82 – 0,98; P = 0,002). Dok vericiguat signifikantno smanjuje hospitalizacije zbog HF-a (HR, 0,90; 95 % CI, 0,81 – 1 ,00), CV smrtnost se nije znatnije smanjila. Nepoželjni su događaji slični kod skupine na vericiguatu i placebu. Nadalje, proučavana je usporedba omjera rizika i apsolutnoga relativnog rizika u trima velikim nedavno objavljenim studijama s bolesnicima u HFrEF-u. Analiza omjera rizika pokazuje manji učinak liječenja u studiji *VICTORIA* nego u *DAPA-HF* i *PARADIGM-HF*, dok usporedba događaja tijekom 12 mjeseci za primarni ishod naglašava

0.86; *P* < 0.001), the secondary endpoints of total HF hospitalizations (HR, 0.70; 95% CI, 0.58–0.85; *P* < 0.001), the annual rate of decline in the estimated glomerular filtration rate (–0.55 vs. –2.28 mL/min/1.73 $m^2$ of body-surface area per year, *P* < 0.001), the risk of serious renal outcomes,[115] and the risk and total number of inpatient and outpatient worsening HF events, which starts early after the initiation of treatment and remains during the duration of treatment.[116] These beneficial effects were also observed to a similar extent in patients pre-treated with ARNI[117] and were independent of baseline diabetes status and across the continuum of HbA1c,[118] and in patients with and without CKD and regardless of the severity of kidney impairment at baseline.[119]

In the SUGAR-DM-HF study, empagliflozin reduced LV volumes measured by CV magnetic resonance in patients with HFrEF and type 2 diabetes or prediabetes.[120] The mechanistic trial EMPA-TROPISM (ATRU-4) showed the beneficial effect of empagliflozin in improving LV volumes, LV mass, LV systolic function, functional capacity, and quality of life in non-diabetic patients with HFrEF[121] (ref). Taken the evidence together, SGLT-2 inhibitors reduce all-cause and CV mortality and improve renal outcomes in patients with HFrEF, supporting the role of dapagliflozin and empagliflozin as a new standard of care for patients with HFrEF.[119,122]

Sotagliflozin, another SGLT-2 inhibitor that displays also gastrointestinal SGLT-1 inhibition and thus reduces intestinal glucose absorption, was investigated in patients with type 2 diabetes after a recent hospitalization for worsening heart failure (SOLOIST-WHF). Patients were included independent of their ejection fraction, and 78% of patients had an ejection fraction <50%. The primary endpoint of CV death, total hospitalizations, and urgent visits for HF was significantly reduced in patients treated with sotagliflozin (HR, 0.67; 95% CI, 0.52–0.85; *P* < 0.001). The results were consistent among subgroups and especially also in patients with an EF > 50%.[123] Sotagliflozin was also investigated in patients with type 2 diabetes, chronic kidney disease, and elevated CV risk (SCORED);[124] primary endpoint (changed during the study to a composite of CV death, total HF hospitalizations and urgent visits for HF) was significantly reduced in patients treated with sotagliflozin (HR, 0.67; 95% CI, 0.52–0.85; *P* < 0.001). It has to be mentioned that both sotagliflozin trials had to be stopped earlier than planned because of loss of funding from the sponsor.

## ACTIVATORS OF SOLUBLE GUANYLATE CYCLASE (VICTORIA, VITALITY, CAPACITY)

The activator of soluble guanylate cyclase (sGC) vericiguat was investigated in the VICTORIA study in 5050 patients with recently decompensated chronic HF and LVEF < 45%.[125,126] Vericiguat significantly reduced the primary outcome of CV death or first HF hospitalisation (HR, 0.90; 95% CI, 0.82–0.98; *P* = 0.02). While vericiguat significantly reduced HF hospitalisations (HR, 0.90; 95% CI, 0.81–1.00), CV deaths were not significantly diminished. Adverse events were largely similar among the vericiguat and placebo groups. An analysis comparing HRs and absolute RR in three large recent HFrEF trials demonstrated that while the HR suggests a smaller treatment effect in VICTORIA than in the DAPA-HF and PARADIGM-HF trials, a comparison of 12-month event rates for the primary outcome pointed to a comparable benefit

usporedivu korist tijekom svih triju studija.[127,128] Postoji značajna interakcija učinaka vericiguata prema bazalnim vrijednostima NTproBNP-a. *Post hoc* analiza pokazuje povezanost dobrobita vericiguata u smislu primarnog ishoda u bolesnika sa vrijednostima NT-proBNP-a do 8000 pg/mL, uz najveću dobrobit u onih s vrijednostima NTproBNP-a <4000 pg/mL (HR, 0,77, 95 % CI, 0,68 – 0,88).[129]

Vericiguat se proučavao u bolesnika s HFpEF-om u studiji *VITALITY*.[128] Nađeno je da nema povoljnog učinka na kvalitetu života i podnošenje napora.[130] Slično tomu, u studiji *CAPACITY* praliciguat lijek iz skupine sGC stimulatora dobro se tolerirao, no nije bilo utjecaja na primarni cilj – učinak na vršnu potrošnju kisika ($pVO_2$), niti druge predefinirane ishode.[131]

### AKTIVATORI I INHIBITORI MIOZINA

#### Omecamtiv mecarbil (studije *GALACTIC-HF, EXPLOER-HCM*)

Aktivator srčanog miozina *omecamtiv mecarbil*, koji mijenja kardiomiocitnu kontrakciju, daje se dvaput na dan na temelju vrijednosti lijeka u plazmi, signifikantno smanjuje primarni cilj (hospitalizacije poradi HF i CV smrtnost) u bolesnika sa HFrEF i nedavnim događajem vezanim za HF (HR, 0,92; 95% CI, 0,86-0,99; P = 0,03), no nema utjecaj na bilo koji sekundarni cilj (CV smrtnost, promjene u stupnjevanju simptoma, prva hospitalizacija zbog HF-a, ukupna smrtnost).[132]

Sličan lijek, danicamptiv, povećava udarni volumen, povećava globalno longitudinalno i circumferencijalno naprezanje, smanjuje minimalni volumni indeks LA, a povećava funkcijski indeks LA kada se uspoređuje s placebom u manjoj kliničkoj studiji 2a faze na 40 bolesnika sa stabilnom HFrEF.[133] S druge strane, mavacamten, miozin inhibitor, znatno poboljšava kombinirani primarni cilj, parametar povećanja vršne potrošnje kisika uz snizivanje NYHA stadija, u fazi 3 kliničke studije, u bolesnika s opstruktivnom hipertrofičnom kardiomiopatijom. Također se poboljšava nalaz opstrukcije izlaznoga trakta LV-a, kao i klinički nalaz.[134]

## Ostala terapija

### ŽELJEZNA KARBOKSIMALTOZA (STUDIJA *AFFIRM-AHF*)

U bolesnika s nedostatkom željeza, hospitaliziranih zbog akutnog HF-a (*AFFIRM-AHF*)[135], intravenska primjena željezne karboksimaltoze u usporedbi s placebom, povezana je sa sniziavanjem ukupnoga broja hospitalizacija zbog HF-a i CV smrtnosti (RR 0,79, 95 % CI 0,62 – 1,01, P = 0,059). U prespecificiranoj analizi, u vremenu pandemije COVID-a 19, nađena je statistički značajna razlika u korist željezne karboksimaltoze za primarni cilj, ali ne i u smrtnosti zbog rizika od CV smrtnosti.[136]

### MIRCORNA-132 INHIBICIJA

U prvome kliničkom pokusu ograničenom na malom broju bolesnika s HF-om, lijek CDR132L antisence oligonucleide, usmjeren izravno protiv miR-132,[137] dobro se tolerirao uz poboljšanje funkcije srca.[138]

### CJELOKUPNA FARMAKOLOŠKA TERAPIJA KOJA PREINAČUJE TIJEK BOLESTI

Koristeći se podatcima iz studija *EMPHASIS-HF, PARADIGM-HF* i *DAPA-HF*, analiziralo se preživljavanje uz cjelokupnu te-

across the three trials.[127,128] Given the significant interaction of vericiguat effects according to baseline NT-proBNP levels, a *post hoc* analysis showed an association of vericiguat benefit on the primary outcome in patients with NTproBNP levels up to 8000 pg/mL, with greatest benefit in patients with NTproBNP <4000 pg/mL (HR, 0.77, 95% CI, 0.68–0.88).[129]

Vericiguat was evaluated In HFpEF patients in the VITALITY trial,[128] showing no benefit in quality of life and exercise tolerance.[130] Similarly, in the CAPACITY trial, the sGC stimulator praliciguat was well-tolerated but did neither affect the primary efficacy endpoint of $pVO_2$ nor other predefined outcome parameters.[131]

### CARDIAC MYOSIN ACTIVATORS AND INHIBITORS

#### Omecantiv mecarbil (GALACTIC-HF, EXPLORER-HCM)

Omecamtiv mecarbil, a cardiac myosin activator that enhances cardiomyocyte contraction, given twice daily on the basis of plasma levels of the drug, significantly reduced the primary endpoint of HF hospitalisation and CV death in patients with HFrEF and a recent HF event (HR, 0.92; 95% CI, 0.86–0.99; P = 0.03) but had no impact on any of the secondary outcomes (CV death, change in symptom score, first HF hospitalization, and death from any cause).[132]

A similar compound, danicamtiv, increased stroke volume, improved global longitudinal and circumferential strain, decreased LA minimal volume index, and increased LA function index when compared to placebo in a small phase 2a trial in 40 patients with stable HFrEF.[133]

On the other hand, mavacamten, a myosin inhibitor, significantly improved the combined primary endpoint of increase in peak oxygen consumption ($pVO_2$) and reduction in NYHA class in a phase 3 trial in patients with obstructive hypertrophic cardiomyopathy. Also, outflow tract obstruction and health status were improved.[134]

## Other therapies

### FERRIC CARBOXYMALTOSE (AFFIRM-AHF)

In iron-deficient patients hospitalized for acute HF (AFFIRM-AHF),[135] intravenous ferric carboxymaltose compared to placebo was associated with a trend to reduced total HF hospitalizations and CV death (rate ratio 0.79, 95% CI 0.62–1.01, *P* = 0·059). In a pre-specified sensitivity analysis considering the impact of the COVID-19 pandemic, a statistically significant difference in favour of ferric carboxymaltose was reported for the primary endpoint was reported, but not in CV death risk.[136]

### MICRORNA-132 INHIBITION

In a first clinical trial limited by a small number of HF patients, the antisense oligonucleotide drug directed against miR-132, CDR132L,[137] was well tolerated and showed first hints for a cardiac functional improvement.[138]

### COMPREHENSIVE DISEASE-MODIFYING PHARMACOLOGICAL THERAPIES

Using data from the EMPHASIS-HF, PARADIGM-HF, and DAPA-HF trials lifetime gains in survival have been estimated with comprehensive therapy (SV, β-blocker, MRA, and SGLT-2

meljnu terapiju (SV, beta-blokatore, antagoniste mineralokortikoidnih receptora i SGLT-2 inhibitore) spram grupe RAAS lijekova i beta-blokatora u bolesnika s kroničnim HFrEF-om.[11,139] Omjer rizika za zajednički cilj (CV smrtnost ili hospitalizacije zbog HF-a) iznosio je 0,38 (95 % CI 0,30 – 0 ,47). Povoljni su rezultati također bili uočeni za CV smrtnost, hospitalizacije zbog HF-a, kao i za ukupnu smrtnost. Cjelokupna farmakološka terapija može produljiti preživljavanje oko 6,3 godine u bolesnika prosječne dobi 55 godina. Ovakav rezultati podržavaju primjenu kombinirane uporabe SV-a, beta-blokatora, antagonista mineralokortikoidnih receptora i SGLT-2 inhibitora kao novi terapijski standard.

## Liječenje intervencijama/uređajima

### SEKUNDARNA (ILI FUNKCIONALNA) MITRALNA REGURGITACIJA (STUDIJA *COAPT*)

Sekundarna (ili funkcionalna) mitralna regurgitacija (SMR) pojavljuje se često u bolesnika s HFrEF-om, a povezana je s progresivnom simptomatologijom i pogoršanjem prognoze. Ako se SMR tretira pristupom „edge-to-edge", bolesnici s optimalnim rezultatima pri otpustu i pri 12-mjesečnom praćenju pokazuju najbolji ishod.[140]

### SRČANA RESINKRONIZACIJSKA TERAPIJA (STUDIJA *STOP-CRT*)

Srčana resinkronizacijska terapija (studija *STOP-CRT*) sastavni je dio liječenja bolesnika s HFrEF-om, posebno uz blok lijeve grane i široki QRS-kompleks. U selekcioniranoj skupini bolesnika s LVEF-om >50% uz CRT i neurohormonalnu blokadu iz studije *STOP-CRT*, proučavane su sigurnost i izvedivost prekidanja neurohormonalne blokade. Incidencija lošijeg remodeliranja LV-a ili kliničkih rezultata bila je mala nakon prekida beta-blokade/RAAS inhibicije. No, komorbiditeti potiču nastavak neurohumoralne blokade u mnogih bolesnika.[141]

U bolesnika s HFrEF-om, ako nisu bili pogodni za CRT, barorefleksna aktivacijska terapija (BAT) može biti korisna kao dodatak optimalnoj primjeni lijekova. U istraživanju *BeAT-HF* BAT je bila sigurna terapija i znatno je poboljšala učestalost simptoma, kvalitetu života, podnošenje napora, kao i vrijednost NT-proBNP.[142] Na temelju navedenih podataka, BAT je odobren u SAD-u, dok će praćenje rezultata *BeAT-HF* studije pokazati učinak na značajne ishode.

## Specifična liječenja

### TELEMEDICINA I DRUGE VRSTE PRAĆENJA NA DALJINU

Uloga telemedicine i praćenja na daljinu u liječenju bolesnika s HF-om još je uvijek proturječna. Opservacijska studija iz triju europskih zemalja, pokazuje da je liječenje HF-a vođeno monitoriranjem plućnoga arterijskoga tlaka (PAP) izvedivo i sigurno i povezano s boljim hemodinamskim i kliničkim ishodima.[143] Osim toga, preliminarni rezultati testiranja neinvazivnoga daljinskoga fiziološkog monitoriranja s pomoću nosivog senzora imaju obećavajuće rezultate u ranom otkrivanju potencijalne rehospitalizacije zbog HF-a.[144] No različiti modeli monitoriranja na daljinu nisu pokazali pozitivne učinke u poboljšanju liječenja i kvalitete života[145] ili pak kliničkih ishoda.[146] Monitoriranje bolesnika na daljinu s implantiranim

inhibitor) vs. RAAS and β-blockers in patients with chronic HFrEF.[11,139] The HR for the composite endpoint of CV death or hospitalisation for HF was 0.38 (95% CI 0.30–0.47). Favourable results were also calculated for CV death alone, hospitalization for HF alone, and all-cause mortality. Comprehensive therapy could prolong overall survival 6.3 years in average in a 55-year-old patient. These results support the combination use of SV, β-blockers, mineralocorticoid receptor antagonists, and SGLT-2 inhibitors as a new therapeutic standard.

## Device/interventional therapies

### SECONDARY (OR FUNCTIONAL) MITRAL REGURGITATION (COAPT)

Secondary (or functional) mitral regurgitation (SMR) occurs frequently in HFrEF and is associated with progressive symptoms and worse prognosis. If SMR is treated by edge-to-edge repair, patients with optimal result at discharge and 12-month follow-up displayed best outcomes.[140]

### CARDIAC RESYNCHRONIZATION THERAPY (STOP-CRT)

Cardiac resynchronization therapy (STOP-CRT) is an integral part of treatment in patients with HFrEF, especially with left bundle branch block and wide QRS. In a selected cohort of patients with LVEF >50% during CRT and neurohormonal blockade, the STOP-CRT study investigated the feasibility and safety of neurohormonal blocker withdrawal. The incidence of adverse LV remodelling or clinical outcomes was low after discontinuation of betablockade/RAAS inhibition. However, comorbidities prompted the continuation of neurohormonal blockers in many patients.[141]

In patients with HFrEF who are ineligible for CRT, baroreflex activation therapy (BAT) may be useful in addition to optimal drug therapy. In the BeAT-HF study, BAT was safe and significantly improved symptoms, quality of life, exercise capacity, and NT-proBNP.[142] On the basis of these data, BAT was approved in the USA, while ongoing follow-up in the BeAT-HF study will assess effects on hard outcomes.

## Specific management issues

### TELEMEDICINE AND REMOTE MONITORING

The role of telemedicine and remote monitoring in the management of HF patients is still controversial. An observational study in three European countries showed that pulmonary artery pressure-guided HF management is feasible and safe and associated with better outcomes haemodynamic and clinical outcomes.[143] Also, preliminary results testing non-invasive remote physiological monitoring from a wearable sensor showed promising results in the early detection of impending HF rehospitalisation.[144] However, different modes of remote monitoring failed to show a benefit in improving treatment, quality of life,[145] or clinical outcomes.[146] Moreover, remote monitoring with a cardiac implanted electronic device increased clinical activity for patients with HF and AF, with no associated reduction in mortality, and conversely, greater risk of CV hospitalisation amongst patients with persistent/permanent AF.[147] In the COVID-19 era, remote monitoring is a useful tool for managing HF patients.[148]

elektroničkim uređajem srca, povećava kliničku aktivnost bolesnika s HF-om i fibrilacijom atrija, no nije povezano sa smanjenjem smrtnosti, a povezano je s većim rizikom od CV hospitalizacija kod bolesnika sa perzistentnom/permanentnom fibrilacijom atrija.[147] U eri COVID-a 19 monitoriranje na daljinu može biti korisno u liječenju bolesnika s HF-om.[148]

## BRIGA O SEBI I PALIJATIVNA NJEGA

Briga o sebi esencijalna je u liječenju kroničnog HF-a. Praktični savjeti za ključne aktivnosti i prioritete opisani su u članku Europskog društva za zatajivanje srca (HFA).[149] Pri kraju kontinuuma bolesnika s HF-om, palijativnu bi brigu trebalo uvesti što prije, usredotočujući se na liječenje simptoma,[150] neovisno o prognozi, što se za sada u Europi malo primjenjuje.[151] Provođenje palijativne njege smanjuje broj hospitalizacija, no učinak na preživljenje nije toliko jasan.[152]

## SELF-CARE AND PALLIATIVE CARE

Self-care is essential in the management of chronic HF. Practical advice for key activities and priorities for self-care is given in an HFA manuscript.[149] At the end of the HF pathway, palliative care should be introduced early, focusing on symptom management,[150] regardless of prognosis, but actually only a minority in Europe receive it.[151] Providing palliative care substantially reduces hospitalizations, with no clear adverse effect on survival.[152]

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