Godina 2021. u kardiovaskularnoj medicini: zatajivanje srca i kardiomiopatije

The year in cardiovascular medicine 2021: heart failure and cardiomyopathies

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SAŽETAK: U 2021.godini objavljena je Univerzalna definicija i klasifikacija zatajivanja srca (HF) koja HF definira kao klinički sindrom sa simptomima i/ili znakovima koje uzrokuje poremećaj srca i potvrđen povišenim vrijednostima natrijuretskog peptida ili objektivnim pokazateljima kongestije. Ova definicija i klasifikacija HF-a sa sniženom ejekcijskom frakcijom (HFrEF), blago sniženom, i HF-a s očuvanom ejekcijskom frakcijom (HFpEF) u skladu je sa Smjernicama Europskog kardiološkog društva (ESC) za HF. Među ostalim novim preporukama, te su smjernice dale klasu I. preporuke za uporabu inhibitora natrij-glukoza kotransportera 2 (SGLT2) dafagliglozina i emfagliflozina u bolesnika s HFrEF-om. Kao prva terapija utemeljena na dokazima za HFpEF, u istraživanju *EMPORER-Preserved*, empagliflozin je smanjio zajednički ishod kardiovaskularne smrti i hospitalizacija zbog HF-a. Više radova u 2021. godini pridonijelo je novom i cjelovitom pristupu liječenju HF-a, posebice sakubitril/valsartan, SGLT2 inhibitori, antagonisti mineralokortikosteroidnih receptora, željezove karboksimaltoze, aktivatori solubilne gvanilat ciklaze i aktivatora srčanog miozina. U bolesnika hospitaliziranih zbog bolesti COVID-19, akutni HF i oštećenje miokarda vrlo su česti, dok su miokarditis i dugotrajna oštećenja srca prilično rijetka pojava.

SUMMARY: In the year 2021, the universal definition and classification of heart failure (HF) was published that defines HF as a clinical syndrome with symptoms and/or signs caused by a cardiac abnormality and corroborated by elevated natriuretic peptide levels or objective evidence of cardiogenic congestion. This definition and the classification of HF with reduced ejection fraction (HFrEF), mildly reduced, and HF with preserved ejection fraction (HFpEF) is consistent with the 2021 ESC Guidelines on HF. Among several other new recommendations, these guidelines give a Class I indication for the use of the sodium–glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin in HFrEF patients. As the first evidence-based treatment for HFpEF, in the EMPEROR-Preserved trial, empagliflozin reduced the composite endpoint of cardiovascular death and HF hospitalizations. Several reports in 2021 have provided novel and detailed analyses of device and medical therapy in HF, especially regarding sacubitril/valsartan, SGLT2 inhibitors, mineralocorticoid receptor antagonists, ferric carboxymaltose, soluble guanylate cyclase activators, and cardiac myosin activators. In patients hospitalized with COVID-19, acute HF and myocardial injury is quite frequent, whereas myocarditis and long-term damage to the heart are rather uncommon.

KLJUČNE RIJEČI: zatajivanje srca, epidemiologija, slikovne metode, biomarkeri, farmakoterapija.

KEYWORDS: heart failure, epidemiology, imaging, biomarkers, pharmacotherapy.

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Uvod

Zatajivanje srca (HF) ostaje velik izazov za bolesnike i zdravstvene sustave širom svijeta. Za bolesnike koji boluju od HF-a sa sniženom ejekcijskom frakcijom (HFrEF) na raspolaganju je liječenje temeljeno na dokazima koje znatno poboljšava prognozu i kvalitetu života; međutim, u dijela takvih bolesnika razvije se brza progresija HF-a usprkos najboljoj skrbi. Nedavno objavljen specijalni članak poziva na akciju za globalnu dostupnost novijih terapijskih mogućnosti liječenja takvih bolesnika,[1] ali isto tako bolesnike s HF-om s očuvanom EF (HFpEF), za koje donedavno nije postojalo nijedno liječenje zasnovano na dokazima.

Introduction

Heart failure (HF) remains a major challenge for patients and healthcare systems worldwide. For patients suffering from HF with reduced ejection fraction (HFrEF), several evidence-based treatments are available and have markedly improved prognosis and quality of life; however, a subset of these patients displays a rapid progression of HF despite best care. A recent special article called to action for global approaches to novel drug solutions for these patients,[1] but also for patients with HF with preserved EF (HFpEF), for whom until recently there was not a single evidencebased treatment.

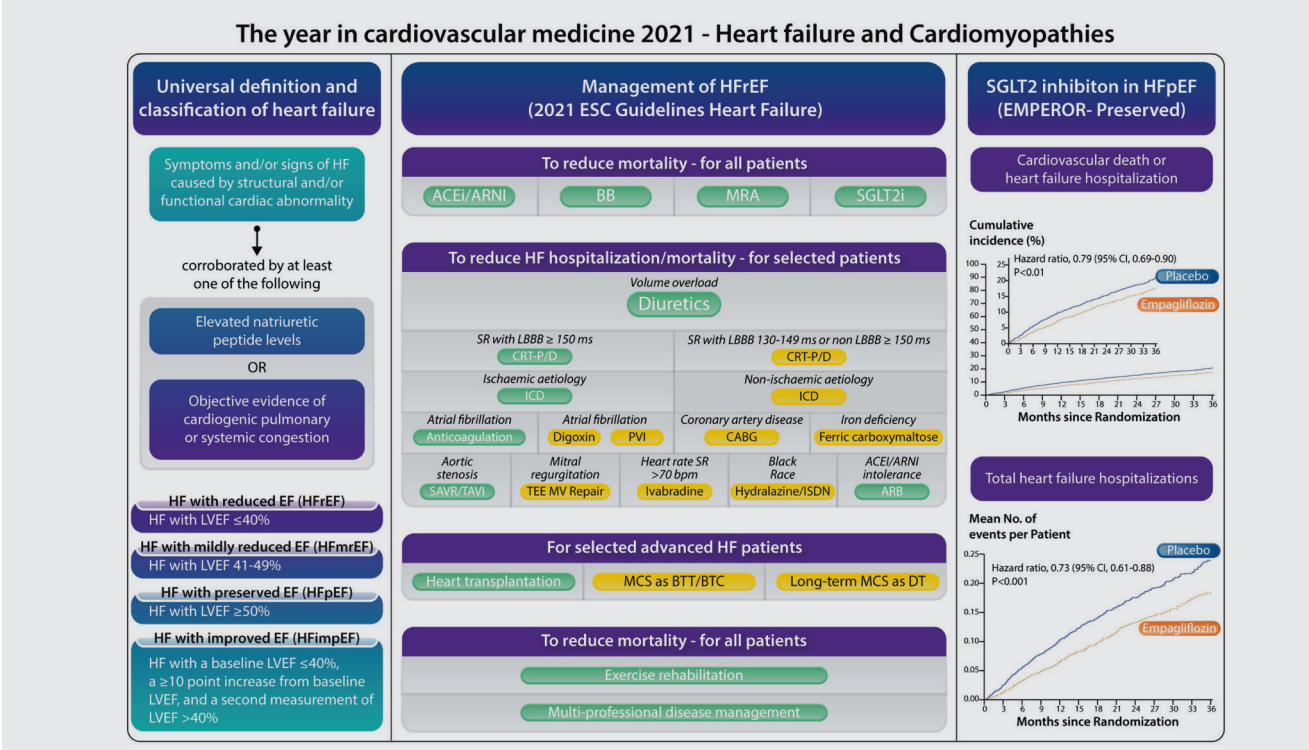

FIGURE 1A GRAPHICAL ABSTRACT. Summary of the universal definition and EF classification of heart failure; management of HFrEF according to 2021 ESC guidelines for heart failure and results of the EMPEROR-preserved trial. (from Bauersachs J, de Boer RA, Lindenfeld J, Bozkurt B. The year in cardiovascular medicine 2021: heart failure and cardiomyopathies. Eur Heart J. 2022 Feb 3;43(5):367-376. doi: 10.1093/eurheartj/ehab887, by permission of OUP on behalf of the ESC).

U ovome članku sažeto je prikazan znatan napredak koji je postignut u 2021. godini glede postavljanja dijagnoze i liječenja HF-a, posebice usmjereno na članke objavljene u časopisima *European Heart Journal* i *European Journal of Heart Failure*.

Definicija i klasifikacija zatajivanja srca

Prepoznajući potrebu za standardizacijom definicije HF-a, stvorena je Univerzalna definicija i klasifikacija zatajivanja srca, koja HF definira kao klinički sindrom s trenutačnim ili prijašnjim simptomima i/ili znakovima koje uzrokuju strukturni i/ili funkcionalni poremećaji srca i potvrđen povišenim vrijednostima natrijuretskog peptida (NP) ili objektivnim pokazateljima kardiogene plućne ili sistemske kongestije uz odgovarajuću dijagnostiku (**slika 1A**).[2] Također je revidirana definicija stupnjeva HF-a, razvrstani su u nekoliko kategorija: *At-Risk for HF* (prije stupanj A) za bolesnike s rizikom od HF-a, ali bez sadašnjih ili prijašnjih simptoma ili znakova HF-a i bez strukturnih promjena srca ili povišenih biomarkera za bolest srca; *Pre-HF* (prije stupanj B) za bolesnike bez sadašnjih ili prijašnjih simptoma ili znakova HF-a, ali s potvrdom strukturne bolesti srca, poremećajem funkcije srca, povišenim vrijednostima NP-a ili troponina; *Heart Failure* (prije stupanj C) za simptomatske bolesnike; *Advanced HF* (prije stupanj D) za bolesnike s teškim simptomima i/ili znakovima HF-a. Kategorije ejekcijske frakcije (EF) lijeve klijetke (LV) podijeljene su (**slika 1A**) u: HFrEF (LVEF ≤40 %), HFmrEF (HF s blago reduciranom EF; LVEF 41 – 49 %), HFpEF (LVEF >50 %) i HFimpEF (HF s poboljšanom EF; početna LVEF ≤40 %, porast ≥10 % od početne LVEF, a u drugom mjerenju LVEF >40 %). Kategorije EF-a rabljene u novim Smjernicama Europskog kardiološkog društva (ESC) za HF iz 2021. u skladu su s ovom klasifikacijom.[3] U „univerzalnoj definiciji HF-a" naglasak je stavljen i na tijek bolesti i uporabu termina „perzistentna HF" umjesto „stabilna HF" za bolesnike s prisutnim simptomima/znakovima i „HF u remisiji" umjesto „oporavljena HF" za bolesnike s povlačenjem simptoma ili znakova HF-a ili s oporavkom prethodne strukturne/funkcionalne bolesti srca[2] (**slika 1B**). Iako je kao druga mogućnost bila predložena jednostavna definicija HF-a prije svega zasnovana na vrijednostima NP-a,[4] ograničenja takvog pristupa zbog varijabilnosti razine NP-a uz dob, spol, tjelesnu težinu, funkciju bubrega i fibrilaciju atrija, nedovoljnu specifičnost i nedostatak dokaza povezanosti liječenja i na biomarkerima temeljenog pristupa, prepoznati su kao znatne prepreke za jednostavan na biomarkerima zasnovan pristup definiciji HF-a.[4]

Epidemiologija

Istraživanje *HF Atlas* pokazalo je širok raspon incidencije HF-a i učestalosti bolničkog liječenja zbog HF-a u Europi sa znatnim razlikama u upravljanju resursima i donijelo kvalitetne podatke koji će omogućiti razvoj strategija za smanjivanje nejednakosti.[5] Izlaganje onečišćivačima zraka povećava rizik od HF-a ovisno o dozi, a rizik od HF-a napose je visok

In this article, we summarize important progress that has been made in 2021 regarding the diagnosis and treatment of HF with a special focus on articles published in 2021 in the *European Heart Journal* and the *European Journal of Heart Failure*.

Definition and classification of heart failure

With the recognition of the need for standardization of an HF definition, the Universal Definition and Classification of Heart Failure was developed, which defined HF as a clinical syndrome with current or prior symptoms and or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide (NP) levels or objective evidence of cardiogenic pulmonary or systemic congestion by diagnostic modalities (**Figure 1A**).[2] It also provided revised definitions for stages of HF, categorized as 'At-Risk for HF' (former Stage A) for patients at risk for HF but without current or prior symptoms or signs of HF and without structural cardiac changes or elevated biomarkers of heart disease; Pre-HF (former Stage B) for patients without current or prior symptoms or signs of HF but evidence of structural heart disease, abnormal cardiac function, elevated NP levels or elevated cardiac troponin levels; 'Heart Failure' (former Stage C for symptomatic patients, 'Advanced HF' (former Stage D) for patients with severe symptoms and/or signs of HF (Figure 1). Ejection fraction categories were classified as HFrEF: left ventricular (LV) EF ≤40% (**Figure 1A**); HF with mildly reduced EF (HFmrEF): LVEF 41–49%; HFpEF: LVEF .50%; and HF with improved EF (HFimpEF): HF with a baseline LVEF ≤40%, a ≥10 point increase from baseline LVEF, and a second measurement of LVEF .40%. The EF categories used in the recent 2021 ESC HF Guidelines were consistent with these classifications.[3] In the Universal Definition of HF, there was also an emphasis on trajectories of HF and to use 'persistent HF' instead of 'stable HF' for patients with ongoing symptoms/signs and 'HF in remission' instead of 'recovered HF' for patients with resolution of symptoms and signs of HF or with the resolution of previous structural/functional heart disease[2] (**Figure 1B**). Though a simple definition of HF predominantly depending on NPs was proposed as an alternative,[4] limitations of such an approach due to variability of NP levels by age, sex, body mass, renal function, and atrial fibrillation; and lack of specificity and lack of evidence in linking treatments to a biomarker-based approach were identified as significant barriers to a simply biomarker-based approach in definition of HF.[4]

Epidemiology

The HF Atlas survey reports a wide-ranging incidence of HF and HF hospitalizations across Europe with considerable heterogeneity in the resources for management and the data quality providing data to allow the development of strategies to improve inequalities.[5] Exposure to ambient air pollutants increases the risk of HF in a dose-dependent fashion, and there was a particularly high risk of HF among persons with

FIGURE 1B. Please see Figure 1 in the original article.

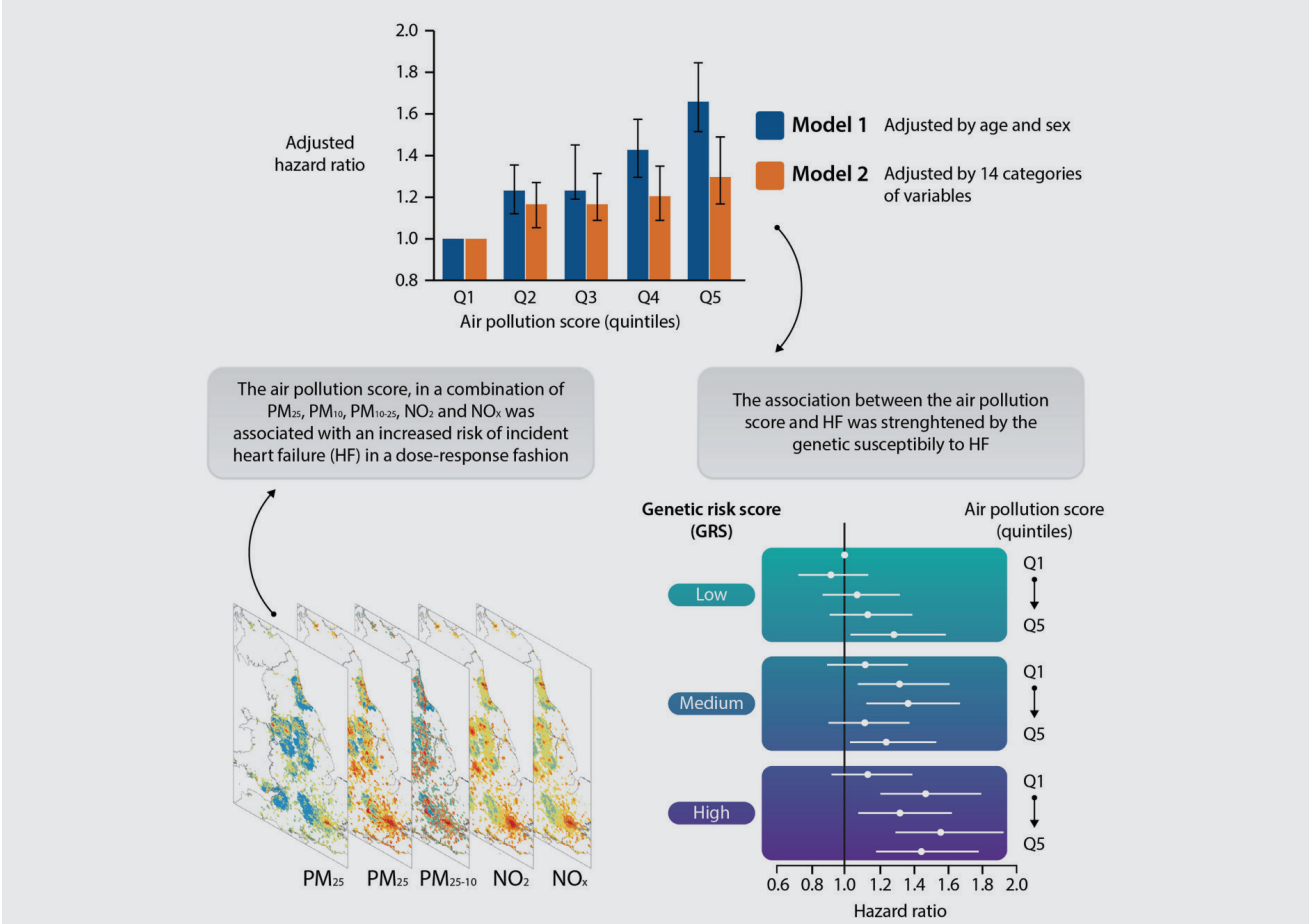

FIGURE 2. Long-term joint exposure to various air pollutants, including PM2.5, PM10, PM2.5–10, NO2, and NOx is associated with an elevated risk of incident heart failure in an additive manner. Persons with genetic higher susceptibility to heart failure displayed a particularly high risk of heart failure. Reprinted with permission from Wang *et al.*[6] (from Bauersachs J, de Boer RA, Lindenfeld J, Bozkurt B. The year in cardiovascular medicine 2021: heart failure and cardiomyopathies. Eur Heart J. 2022 Feb 3;43(5):367-376. doi: 10.1093/eurheartj/ehab887, by permission of OUP on behalf of the ESC).

kod bolesnika s genskom predispozicijom za HF (**slika 2**).[6] Zagađenje zraka vjerojatno bi trebalo biti uvršteno u procjenu rizika za predviđanje HF-a.

Nedavni izvještaj Europskog registra pokazao je da je dilatativna kardiomiopatija (DCM), a ne skeletna miopatija, glavna je odrednica prognoze u bolesnika s mutacijom gena za distrofin.[7] Konačno, karcinom i HF pojavljuju se zajedno mnogo češće nego što je predviđeno modelima rizika, i nedavno objavljeno istraživanje sugerira da statini smanjuju rizik od jednog i drugog i imaju veću redukciju rizika sa što duljim uzimanjem.[8]

Dijagnostika i stratifikacija rizika

Glavni dijagnostički kriterij za HFrEF ostaje LVEF ≤40 %.[3] Međutim, više se raspravlja o ostalim dvjema kategorijama, HFmrEF-u i HFpEF-u. Pieske *i sur.*[9] sastavili su, uime ESC-a, nove dijagnostičke kriterije, uključujući ultrazvučne parametre, vrijednosti NP-a i, ako se ne može postaviti konačna dijagnoza, uputili na provedbu testova opterećenja i/ili invazivnih testove hemodinamike.

genetic higher susceptibility to HF (**Figure 2**).[6] Air pollution probably should be considered in risk scores to predict HF.

A recent European registry report demonstrated that dilated cardiomyopathy (DCM), not skeletal myopathy, is the major determinant of prognosis in patients with dystrophin gene mutations. [7] Finally, cancer and HF occur more commonly together that predicted by risk models, and a recent study suggests that statins reduce the risk of both and have a greater risk reduction with more prolonged use.[8]

Diagnostics and risk stratification

For HFrEF, the main diagnostic criterion remains LVEF ≤40%.[3] However, there is more controversy in the other categories, HFmrEF and HFpEF. Pieske et al.[9] formulated, on behalf of the ESC, new diagnostic criteria, including echo parameters, NPs, and if a definitive diagnosis cannot be made, to turn to stress testing and/or invasive haemodynamics.

There is increasing appreciation that classical diagnostics fall short in complex multifactorial diseases with various aeti-

Raste spoznaja da klasična dijagnostika nije dostatna u komplesnoj multifaktorskoj bolesti s različitim etiologijama i precipitirajućim čimbenicima, a nekoliko je istraživanja bilo usmjereno na to može li agnostički pristup, u kojemu se velika količina podataka ispituje putem kompjuterskih algoritama, biti superiorniji u postavljanju specifične dijagnoze. Takve se tehnike nazivaju strojnim učenjem (ML) i umjetnom inteligencijom (AI). Peyster *i sur.*[10] koristili su se automatskom analizom slika za otkrivanje odbacivanja nakon transplantacije srca i opisali su je kao *Computer-Assisted Cardiac Histologic Evaluation (CACHE)-Grader*, alat koji se pokazao neinferioran u stupnjevanju odbacivanja alatu koji su oblikovali neovisni patolozi. Drugo područje istraživanja za koje AI pruža atraktivne alate jest kategorizacija bolesnika koji su dobili opću dijagnozu HF-a. Verdonschot *i sur.*[11] uključili su u istraživanje podatke o etiologiji i komorbiditetima, slikovnim nalazima i biopsiji endomiokarda od 795 uzastopnih bolesnika s DCM-om te su identificirali četiri različite fenogrupe. Woolley *i sur.*[12], koristeći se algoritmom na bazi 363 biomarkera po fenotipu, u 429 bolesnika s HFpEF-om identificirali su 4 skupine s različitim kliničkim parametrima i znatnom razlikom u prognozi.

Umjetna inteligencija / strojno učenje mogli bi biti korisni za postavljanje dijagnoze HF-a. Kwon *i sur.*[13] obrađivali su podatke 34 103 bolesnika u kojih su obavljene ehokardiografija i elektrokardiogram i kreirali su ML algoritam koji je mogao otkriti HFpEF. Segar *i sur.*[14] koristili su se ML modelima kao pomoći pri predviđanju pojave HF-a uz specifični faktor rizika od rasne pripadnosti.

U bližoj budućnosti bit ćemo suočeni s puno više potencijalnih primjena AI/ML modela, jer postoji jasna potreba za individualnim pristupom i donošenjem odluka.[15] Osnovno je, međutim, dati preporuke koji su ulazni podatci (minimalno) potrebni, a modeli trebaju biti prospektivno ispitani u neovisnim postavkama. Nadalje, odluke o liječenju zasnovane na modelima trebaju biti ispitane na randomizirani slijepi način.[16]

SLIKOVNE METODE I BIOMARKERI

Postavljenje dijagnoze HF-a i dalje ostaje izazov. Smjernice ESC-a preporučuju znakove i simptome, dopunjene slikovnim studijama i biomarkerima. Slikovne se metode primarno odnose na ehokardiografiju i CMR, a preferirani su biomarkeri vrijednosti NP-a i visokosenzitivnih troponina. Sofisticirana klasifikacija bolesnika u različite kategorije, koristeći se slikovnim metodama i biomarkerima, može pospješiti adekvatnu fenotipizaciju[11,17], a oslikavanje nesrčanoga tkiva, poput masnoga tkiva, može također biti relevantno za fenotipizaciju HF-a.[18,19] Novije generacije genskih analiza pokazale su se važnima na prognozu[20] i dijagnozu[21] HF-a. Noviji članci ističu indikacije za biopsiju miokarda.[22]

Specifične situacije

AKUTNO ZATAJIVANJE SRCA

Smjernice ESC-a iz 2021. nisu znatno promijenile preporuke za akutni HF, premda je uporaba opioida degradirana u klasu III. preporuka.[3] Povećava se broj dokaza koji uporabu nalaza natrija u urinu podržavaju u procjeni ishoda u akutnom HF-u.[23,24]

ologies and precipitants, and several studies have addressed whether an agnostic approach, where large data sets are queried by computer algorithms, may be superior in making a specific diagnosis. Such techniques are referred to as machine learning (ML) and artificial intelligence (AI). Peyster et al.[10] used an automated image analysis to detect rejection after heart transplantation and described a 'Computer-Assisted Cardiac Histologic Evaluation (CACHE)-Grader' pipeline that was non-inferior to the rejection grading provided by independent pathologists. Another field of research for which AI provides an attractive tool is the categorization of patients who received a general diagnosis of HF. Verdonschot et al.11 studied 795 consecutive DCM patients with data on aetiology and co-morbidities, imaging studies and endomyocardial biopsies, and identified four distinct phenogroups. Woolley et al.[12] using an algorithm based on 363 biomarkers to phenotype, 429 patients with HFpEF identified four clusters with different clinical parameters and important differences in prognosis.

Artificial intelligence/machine learning might be particularly useful for a diagnosis of HF. Kwon et al.[13] evaluated data from 34 103 patients who underwent echocardiography and electrocardiogram (ECG) and created an ML algorithm that could detect HFpEF. Segar et al.[14] employed ML models to aid in predicting racespecific risk for incident HF.

In the near future, we will be faced with many more potential utility of AI/ML models, as there is a clear need for individualized approaches and decision-making.[15] It will be essential, however, to provide recommendations as to what input is (minimally) required for models, and the models must be prospectively tested in independent settings. Furthermore, treatment decisions based on the models must be tested in a randomized blinded fashion.[16]

Imaging and biomarkers

A state-of-the-art diagnosis of HF remains challenging. The ESC guidelines3 recommend using an array of signs and symptoms, supplemented with imaging and biomarkers studies. The imaging primarily relies on echocardiography and CMR, and NPs and high sensitivity troponins are the preferred biomarkers. However, sophisticated classification of patients in various categories using imaging and biomarkers may enhance adequate phenotyping,[11,17] and imaging of non-cardiac tissues such as fat may have relevance to HF phenotyping, too.[18,19] Furthermore, next-generation genetic analyses has been shown to have a consequence for prognosis[20] and diagnosis[21] of HF. In addition, a recent article highlighted the indications of endomyocardial biopsies.[22]

Specific situations

ACUTE HEART FAILURE

The 2021 ESC guidelines did not significantly change recommendations for acute HF, although the use of opioids was downgraded to a Class III recommendation.[3] Evidence continues to accrue supporting the use of urinary sodium in assessing outcomes in acute HF.[23,24]

KARDIOGENI ŠOK

Mortalitet je i dalje visok u kardiogenom šoku, a randomizirana istraživanja za procjenu liječenja i dalje su rijetkost. Studija iz jednog centra randomizirala je bolesnike s kardiogenim šokom na milrinon ili dobutamin i nije se pokazala nikakva razlika bilo u primarnim bilo u sekundarnim ishodima.[25] U praćenju rezultata istraživanja *IMPRESS* o kardiogenom šoku, nije bilo razlike u smrtnosti nakon 5 godina uspoređujući uporabu intraaortalne balonske pumpe i Impella uređaja.[26] Zbroj biomarkera (cistatin C, laktati, interleukin-6, NT-proBNP) nadmašio je druge procjene rizika za kardiogeni šok.[27] Nedavno je objavljeno zajedničko mišljenje koje je utvrdilo važnost optimizacije istraživanja u kardiogenom šoku.[28]

MEHANIČKA CIRKULACIJSKA POTPORA LIJEVOJ KLIJETKI I TRANSPLANTACIJA SRCA

Registar podataka sakupljanih u jednom centru potvrdio je da su ishodi uz *HeartMate III* (HMIII) bolji od prijašnjih kontrola potvrđujući time randomizirana istraživanja.[29] Učestalost moždanog udara uz HMIII manja je nego uz *Heartware ventricular assist device* (HVAD), što je jedan od nekoliko razloga zbog kojih je HVAD povučen iz primjene.[30] Uporaba mehaničke cirkulacijske potpore lijevoj klijetki (LVAD) ne smanjuje fibrozu miokarda niti novi model procjene rizika poboljšava predviđanje zatajivanja desne klijetke nakon LVAD-a, ali, s druge strane, stariji bolesnici imaju poboljšanje u kvaliteti života i kapaciteta podnošenja napora uz LVAD.[31-33] Postoji značajna interopservacijska varijabilnost pri dijagnozi staničnog odbacivanja kod biopsije miokarda, ali bi automatska kompjuterska analiza slika mogla omogućiti poboljšanje standardizacije, kao što je već to opisano. Neinvazivna predikcija odbacivanja srčanog transplantata nije dostupna, ali istraživanja u kojima se iskorištava izvanstanična DNA periferne krvi pokazuje obećavajuće rezultate u ranoj fazi istraživanja.[34]

TRUDNOĆA / BOLESNICE S PERIPARTALNOM KARDIOMIOPATIJOM

Žene s poznatom kardiomiopatijom ili u riziku od HF-a koje planiraju trudnoću ili se u njih HF očituje tijekom ili nakon trudnoće, trebaju individualnu procjenu i savjetovanje prije, tijekom i nakon trudnoće.[35]

Bolesnice s peripartalnom kardiomiopatijom imaju rizik od nepovoljnih ishoda[36,37], ali se često oporave od HFrEF-a. Nedavne su publikacije istraživale važnost abnormalnosti EKG-a za predikciju ehokardiografskih nalaza i ulogu hipertenzivnih poremećaja tijekom trudnoće.[38,39]

HIPERTROFIJSKA KARDIOMIOPATIJA / AMILOIDOZA

U istraživanju zdravstvenog stanja *EXPLORER-HCM* mavacamten je znatno poboljšao zdravstveno stanje bolesnika sa simptomatskom opstruktivnom hipertrofijskom kardiomiopatijom (HCM) u usporedbi s placebom.[40] Nedostatak dokaza za stratifikaciju rizika od iznenadne srčane smrti kod HCM-a saželi su Pelliccio *i sur.*[41] U istraživanju iz *Sarcomeric Human Cardiomyopathy Registry* Marston *i sur.*[42] u bolesnika u kojih je HCM nastupio u djetinjstvu utvrdili su da vjerojatnije imaju bolest sarkomera, nose veći rizik od za život opasnih aritmija i imaju veću potrebu za uznapredovalim metodama liječenja HF-a. U stručnom mišljenju Njemačkog kardiološkog društva Yilmaz *i sur.*[43] dali su dijagnostički algoritam za otkrivanje

CARDIOGENIC SHOCK

Mortality remains high in cardiogenic shock, and randomized trials assessing therapies remain rare but a single-centre trial randomized patients with cardiogenic shock to either milrinone or dobutamine and showed no differences in any of the primary or secondary outcomes.[25] In the follow-up of the IMPRESS trial in cardiogenic shock, there was no difference in mortality comparing intra-aortic balloon pumps vs. the Impella device at 5 years.[26] A biomarker composite outperformed other risk scores for cardiogenic shock using 4 biomarkers [Cystatin C, Lactate, interleukin-6, and N-terminal pro brain natriuretic peptide (NT-proBNP)].[27] A recent consensus statement outlines important suggestions for optimizing cardiogenic shock trials.[28]

VENTRICULAR ASSIST DEVICES AND HEART TRANSPLANTATION

A single entry registry confirms that HeartMate III (HMIII) outcomes are better than historical controls confirming randomized trials.[29] The stroke rate with HMIII is less than with the Heartware ventricular assist device (HVAD)—one of several reasons the HVAD has been withdrawn from use.[30] Disappointingly, left ventricular assist devices (LVAD) use does not reduce myocardial fibrosis nor does a new risk score improve the prediction of right ventricular failure post-LVAD, but on the bright side, elderly patients have benefits in quality of life and exercise capacity with LVADs.[31–33] There is substantial inter-observer variability in the diagnosis of cellular rejection in myocardial biopsies but automated computation image analysis may allow improved standardization as described in the section on Diagnostics and Imaging. Non-invasive prediction of rejection in cardiac transplant recipients has been elusive, but studies using peripheral blood cell-free DNA show promising early results.[34]

PREGNANCY/PATIENTS WITH PERIPARTUM CARDIOMYOPATHY

Women with a known cardiomyopathy or at risk for HF planning pregnancy, or presenting with HF during or after pregnancy are in need of individualized pre-, during, and post-pregnancy assessment and counselling.[35]

Patients with peripartum cardiomyopathy are at risk for detrimental outcomes[36,37] but often do recover from HFrEF. Recent publications investigated the value of ECG abnormalities for predicting echocardiographic results and the role of hypertensive disorders during pregnancy.[38,39]

HYPERTROPHIC CARDIOMYOPATHY/ AMYLOIDOSIS

In the health status analysis of EXPLORER-HCM, mavacamten markedly improved the health status of patients with symptomatic obstructive hypertrophic cardiomyopathy (HCM) compared with placebo.[40] Gaps in evidence for risk stratification for sudden cardiac death in HCM were summarized by Pelliccia et al.[41] In a study by Marston et al.[42] using Sarcomeric Human Cardiomyopathy Registry, patients with childhood-onset HCM were reported more likely to have sarcomeric disease, carry a higher risk of lifethreatening ventricular arrhythmias, and have a greater need for advanced HF therapies. In the German Cardiac Society position statement, Yilmaz et al.[43] outline a diagnostic algorithm to detect cardiac amyloidosis, to accurately

amiloidoze srca, za precizno određivanje proširenosti i za pouzdano određivanje podvrste amiloidoze, omogućujući time daljnje ciljano liječenje.

KARCINOMI

Zatajivanje srca često komplicira liječenje karcinoma i noviji članak predlaže definicije kardiovaskularne (CV) toksičnosti.[44] Klasično, kemoterapija i radioterapija prepoznate su kao čimbenici rizika, ali u sadašnjim desetljećima imunoterapija imunim *checkpoint* inhibitorima (ICI) postaje osnova liječenja karcinoma. Međutim, ICI isto tako nose povećan rizik od kardiovaskularnih nuspojava. D'Souza *i sur.*[45] objavili su podatke o rizicima u Danskom registru i pokazali su da je primjena ICI-ja povezana s 1,8 %-tnim jednogodišnjim rizikom za (peri)miokarditis, i s gotovo 10 %-tnim rizikom od bilo koju kardiovaskularnu komplikaciju. Uzevši u obzir rastuću uporabu ICI-ja, ova će tema će trebati kliničke smjernice i buduća istraživanja, uz to što ICI-i imaju učinak na više vrsta stanica i tkiva.[46,47] Postoje početne preporuke koje daju upute za liječenje ICI-jima induciranog miokarditisa.[48,49]

U ovom znanstvenom području širi se spoznaja da je pojava karcinoma učestalija u bolesnika u kojih je učestaliji i HF,[50] te da su karcinom i HF možda mnogo više blisko povezani nego što se prije mislilo. Kao podrška tomu, Ren *i sur.*[8] pokazali da uporaba statina smanjuje pojavu karcinoma. U specijalnom članku Zannad *i sur.*[51] raspravljali su o aspektima istraživanja karcinoma koji bi mogli biti primijenjeni u HF-u radi pojednostavnjenja procesa kliničkog istraživanja i smanjenja vremena i troškova potrebnih za dobivanje sigurnih i učinkovitih načina liječenja bolesnika s HF-om.

Farmakoterapija

NOVI ALGORITMI IZ SMJERNICA EUROPSKOGA KARDIOLOŠKOG DRUŠTVA U VEZI S FARMAKOLOŠKIM LIJEČENJEM ZATAJIVANJA SRCA SA SNIŽENOM SISTOLIČKOM FUNKCIJOM LIJEVE KLIJETKE

Prema razini 1 preporuka za farmakološko liječenje, svim bolesnicima s HFrEF-om preporučuje se kombinirano liječenje inhibitorom angiotenzin konvertirajućeg enzima (ACEi) ili angiotenzin receptor neprilizin inhibitorom (ARNI), beta-blokatorom, antagonistom receptora mineralokortikoida (MRA) i inhibitorom natrij-glukoza kotransporter 2 (SGLT2i) (dapagliflozin ili/i empagliflozin) (**slika 1 B**).[3] Smjernice i dalje preporučuju uporabu ARNI-ja kao zamjene za ACEi; no, primjena ARNI-ja može se razmatrati i kao prva linija terapije umjesto ACEi. Savjetuje se da ove četiri skupine lijekova koje mogu modificirati bolest budu početna terapija u vrlo kratkom vremenu susljedne primjene.[3,52] Na potencijalne prednosti drugog algoritma, uz sekvencijalnu primjenu lijekova, upućuju McMurray i Packer[53] s beta-blokatorom i inhibitorom SGLT2-a kao prvom linijom terapije. No takva se terapija s patofiziološkoga stajališta još nije dokazala kao liječenje utemeljeno na dokazima.

Nedavno usuglašeni dokument Udruženja za zatajivanje srca (HFA) ESC-a identificira 9 varijabli koje bi mogle biti relevantne za liječenje bolesnika s HFrEF-om, i to: frekvenciju srca, fibrilaciju atrija, niži arterijski tlak praćen simptomima, procijenjeni stupanj glomerularne filtracije i hiperkalemiju.

determine its extent, and to reliably identify the underlying subtype of amyloidosis, thereby enabling subsequent targeted treatment.

CANCER

Heart failure often complicates the treatment of cancer, and a recent paper proposes definitions of cardiovascular (CV) toxicities. [44] Classically, chemotherapy and radiotherapy have been identified as risk factors, but in the recent decade, immunotherapy with immune checkpoint inhibitors (ICIs) is becoming the mainstay of cancer treatment. However, ICIs also carry a risk for CV side effects. D'Souza et al.[45] reported on this risk in a Danish registry and show that ICI is associated with a 1.8% 1-year risk for (peri-)myocarditis, and with an almost 10% risk for any CV complication. Given the increasing use of ICI, this issue will require clinical guidance and further study, as ICIs have an impact on several cells and tissues.[46,47] There are initial reports providing guidance as to treat ICI-induced myocarditis.[48,49]

This field extends the increasing awareness that incident cancer is more common in patients with prevalent HF,[50] and that cancer and HF may be connected more closely than anticipated before. In support of this, Ren et al.[8] demonstrated that the use of statins reduces incident cancer. Finally, a special article by Zannad et al.[51] discusses aspects of cancer research that may be applicable to HF research, with the aim of streamlining the clinical trial process and decreasing the time and cost required to bring safe, effective, treatments to HF patients.

Pharmacotherapies

NEW ALGORITHM OF THE 2021 ESC GUIDELINES ON HEART FAILURE FOR THE PHARMACOLOGICAL TREATMENT OF HEART FAILURE WITH REDUCED EJECTION FRACTION

The 2021 ESC Guidelines on HF provide a Class I recommendation for pharmacological treatment of all HFrEF patients with a combination of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor–neprilysin inhibitor (ARNI), a betablocker, a mineralocorticoid receptor antagonist (MRA), and a sodium–glucose co-transporter 2 (SGLT2) inhibitor (dapagliflozin or \and empagliflozin) (**Figure 1B**).[3] The guideline still recommends the use of ARNI as a replacement for ACE inhibitor; however, an ARNI may also be considered as a first-line therapy instead of an ACE inhibitor. It is recommended that these four diseasemodifying drugs are initiated within a short time frame.[3,52] Potential advantages of another algorithm for the sequencing of these drugs have been suggested by McMurray and Packer[53] with beta-blockade and SGLT2 inhibition as first-line therapies. However, albeit appealing from a pathophysiological standpoint such a new sequence is not yet evidence-based.

A recent consensus document of the HFA of the ESC identified nine patient profiles that may be relevant for treatment implementation in patients with HFrEF taking into account heart rate, atrial fibrillation, symptomatic low blood pressure, estimated glomerular filtration rate, or hyperkalaemia. Using such a personalized approach may lead to a better and more comprehensive therapy for each individual patient.[54]

Personalizirani bi pristup mogao dovesti do bolje i sveuobuhvatnije terapije za svakog bolesnika.[54]

INHIBITORI ANGIOTENZIN KONVERTIRAJUĆEG ENZIMA

ACE inhibitori već su godinama standard u prevenciji i liječenju zatajivanja srca (HF), no utjecaj ovih lijekova u bolesnika s Duchenneovom muskularnom distrofijom i HF-om nije posve jasan. Veliki Francuski registar pokazao je da profilaktičko liječenje uz ACEi u bolesnika bez disfunkcije lijeve klijetke može spriječiti prelazak u fazu HF-a, a usto poboljšava i preživljavanje u Duchenneovoj muskularnoj distrofiji.[55]

ANGIOTENZIN RECEPTOR NEPRILIZIN INHIBITORI (PARAGON, PARADIGM, PARALLAX, PARADISE-MI, LIFE)

U analizi istraživanja *PARADIGM-HF* početno liječenje sakubitril/valsartanom, čak i ako se titrira do ciljne doze, ne vodi do znatnijeg prekidanja ili smanjivanja titracije drugih lijekova u skladu sa smjernicama, a povezano je s manjim prekidanjem primjene MRA-a.[56] U bolesnika s HFrEF-om u svakodnevnoj je praksi primjena sakubitril/valsartana učinkovita, sigurna i dobro podnošljiva.[57-60] Sakubitril-valsartan je pokazao značajnu korist u liječenju rezistentne hipertenzije u bolesnika s HFpEF-om u istraživanju *PARAGON-HF* u usporedbi s valsartanom.[61] U istraživanju *PROVE-HF* u bolesnika s HFrEF-om vrijednost EF-a se poboljšala (na >35 %) u 32 % ispitanika nakon 6 mjeseci, odnosno u 62 % bolesnika nakon 12 mjeseci od početka primjene sakubitril/valsartana.[62] U bolesnika s asimptomatskom sistoličkom disfunkcijom lijeve klijetke, nakon infarkta miokarda, liječenje sakubitril/valsartanom nije dovelo do znatnog remodeliranja u usporedbi s valsartanom.[63,64] U istraživanju *PARADISE-MI*[65] primjena sakubitril/valsartana nije znatno smanjila učestalost KV smrtnosti, hospitalizacije zbog HF-a ili liječenja ambulantnih bolesnika s HF-om u kojih su vrijednosti LVEF-a ≤40 % i/ili s pulmonalnom kongestijom nakon akutnog infarkta miokarda, u usporedbi s ramiprilom (rezultati prikazani na Kongresu ACC-a). U istraživanju *Sakubitril/Valsartan in Patients with Advanced Heart Failure with Reduced Ejection Fraction in the Advanced Heart failure* (*LIFE-HF*) koje je uključivalo bolesnike u NYHA IV. stupnju s vrijednostima LVEF-a ≤35 %, primjena sakubitril/valsartana nije poboljšala zajedničke kliničke ishode (prikazano na ACC-u 2021.). Rezultati istraživanja *PARALLAX* odredit će poboljšava li primjena sakubitril/valsartana vrijednosti NT-proBNP-a, kapacitet vježbanja, kvalitetu života i simptome u bolesnika s HF-om u kojih je LVEF >40 %.[66]

U novim Smjernicama ESC-a o zatajivanju srca 2021.[3] sakubitril/valsartan preporučuje se kao nadomjesna terapija za ACEi u bolesnika s HFrEF-om, i to kao razina 1 preporuke. Započinjanje liječenja sakubitril/valsartanom u bolesnika s HFrEF-om koji ne uzimaju ACEi ubraja se u razinu 2 B preporuke.[3]

INHIBITORI NATRIJ-GLUKOZA KOTRANSPORTER 2 (EMPEROR-REDUCED, EMPEROR-PRESERVED, DAPA-HF, SOLOIST)

Inhibitori natrij-glukoza kotransporter 2 čine skupinu lijekova rastuće važnosti, koji se mogu uporabljivati u širokom spektru kardiometaboličkih i renalnih bolesti. U istraživanjima u bolesnika s tipom 2 dijabetesa utvrđen je povoljan učinak što se

ANGIOTENSIN-CONVERTING ENZYME INHIBITION

While ACE inhibitors are a standard for the prevention and treatment of HF for many years, the impact of these drugs as preventive therapy for HF in patients with Duchenne muscular dystrophy was unclear. A large French registry showed that prophylactic treatment of patients without LV dysfunction with an ACE inhibitor was able to prevent the transition to HF and improve survival in Duchenne muscular dystrophy.[55]

ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITORS (PARAGON, PARADIGM, PARALLAX, PARADISE-MI, LIFE)

In an analysis of the PARADIGM-HF trial, initiation of sacubitril/valsartan, even when titrated to target dose, did not lead to greater discontinuation or down-titration of other guideline-directed medical therapies and was associated with fewer discontinuations of MRA.[56] In real-world patients with HFrEF, sacubitril/valsartan was effective, safe, and well tolerated.[57–60] Sacubitril–valsartan was found to be useful in treating resistant hypertension in HFpEF in the PARAGON-HF trial when compared with valsartan.[61] In the PROVE-HF trial, in patients with HFrEF, 32% improved their EF to > 35% by 6 months and 62% to > 35% by 12 months after initiation of sacubitril/valsartan therapy.[62] In patients with asymptomatic LV systolic dysfunction late after myocardial infarction, treatment with sacubitril/valsartan did not have a significant reverse remodelling effect compared with valsartan.[63,64] In the PARADISE-MI trial,[65] sacubitril/valsartan did not significantly reduce the rate of CV death, HF hospitalization, or outpatient HF requiring treatment in patients with LVEF ≤40% and/or pulmonary congestion following acute myocardial infarction, compared with ramipril (results presented at the ACC). In the Sacubitril/Valsartan in Patients with Advanced Heart Failure with Reduced Ejection Fraction in the Advanced Heart Failure (LIFE-HF) trial, which enrolled NYHA Class IV patients and LVEF ≤35%, sacubitril/valsartan did not improve the clinical composite endpoints (presented at ACC 2021). PARALLAX trial will determine if sacubitril/valsartan improves NT-proBNP levels, exercise capacity, quality of life, and symptom burden in HF patients with EF > 40%.[66]

In the new 2021 ESC Guidelines on HF,[3] sacubitril/valsartan is recommended as a replacement for an ACE inhibitor in patients with HFrEF as a Class I recommendation. Initiation of sacubitril/valsartan in ACE inhibitor naive patients with HFrEF on the other hand is suggested as a Class IIb recommendation.[3]

SODIUM–GLUCOSE CO-TRANSPORTER 2 INHIBITORS (EMPEROR-REDUCED, EMPEROR-PRESERVED, DAPA-HF, SOLOIST)

Sodium–glucose co-transporter 2 inhibitors are rapidly becoming the panacea for the entire spectrum of cardiometabolic and renal disease. In trials in type 2 diabetes mellitus (T2DM), a beneficial effect was observed for CV endpoints in general, while the effects on incident HF were overwhelmingly positive. These effects were validated in patients with prevalent HFrEF, first in DAPA-HF and a year later in the EMPEROR-Reduced trial. Numerous subanalyses from these trials were published in 2021.

tiče KV ishoda, dok je rezultat na pojavnost zatajivanja srca bio pretežito pozitivan. Učinci su bili proučavani u bolesnika koji su imali veću prevalenciju HFrEF-a, prvo u istraživanju *DAPA-HF*, a godinu poslije u istraživanju *EMPEROR-Reduced*. Tijekom 2021. objavljene su brojne subanalize spomenutih istraživanja.

Osim učinaka na glavne ishode, sve se više uočava važnost funkcionalnog statusa i simptoma u bolesnika s HFrEF-om.[67] Oba su istraživanja (*DAPA-HF* i *EMPEROR-Reduced*) upozorila na njegovo poboljšanje[68,69], dok manje istraživanje s empagliflozinom nije pokazao poboljšanje funkcionalnoga statusa.[70] Serija subanaliza nije pokazala interakciju inhibitora SGLT2-a s uobičajnim lijekovima za liječenje HF-a (MRA), kao ni sakubitril/valsartanom.[71,72] Nadalje, jednak je učinak uočen ne samo kod lijekova nego i u različitim zemljama i etničkim skupinama.[73] Druga važna opservacija koja je uočena kod dapagliflozina jest povezanost s nižom incidencijom novonastalog dijabetesa.[74] Do trenutka objave ove publikacije nijedna analiza nije pokazala različitu ili manje učinkovitu ulogu inhibitora SGLT2 u bolesnika s HFrEF-om. Stoga je važno poraditi na praktičnoj implementaciji ovih lijekova.[52,75]

Za razliku od HFrEF-a, učinkovitost inhibitora SGLT2 u HFpEF ostaje u fazi dokazivanja. No istraživanje *EMPEROR-Preserved*, prikazano tijekom Kongresa ESC-a 2021., pokazalo je da empagliflozin reducira primarni zajednički ishod (KV smrtnost i hospitalizacije zbog HF-a) u gotovo 6000 bolesnika s HFpEF-om (**slika 3**). Ovi su rezultati izuzetno važni i pružaju nadu za milijune bolesnika s HFpEF-om za koje do sada nije bilo na dokazima utemljenog liječenja. Tijekom medijana praćenja od 26 mjeseci primarni se ishod pojavio u 13,8 % ispitanika u skupini na empagliflozinu i u 17,1 % ispitanika u skupini na placebu (HR: 0,79; 95% CI: 0,69 –0,90; p <0,001). Empagliflozin je bio vrlo učinkovit u smanjenju hospitalizacije zbog HF-a, no ukupna se smrtnost nije smanjila. Ovakav je učinak bio prisutan u bolesnika neovisno o prisutnosti tipa 2 dijabetesa.[76,77] Rezultati istraživanja *DELIVER* koje je pratilo smrtnost u HFpEF-u uz primjenu dapagliflozina bit će uskoro prikazani.[78]

Inhibitori natrij-glukoza kotransporter 2 također se ispituju u bolesnika s akutnim HF-om ili odmah nakon akutne dekompenzacije. Istraživanje *SOLOIST*[79] sa sotagliflozinom (kombinirani dvostruki inhibitor SGLT1 i SGLT2) uključilo je 1244 bolesnika s tipom 2 dijabetesa i nedavnim pogoršanjem HF-a. Dokazan je povoljan učinak lijeka primijenjenog prije ili kratko nakon otpusta, uz znatno smanjenje ukupnoga broja KV smrti i hospitalizacija zbog HF-a, kao i urgentnih pregleda zbog iste bolesti. Istraživanje *EMPULSE* donijet će više novih podataka iz područja akutnog HF-a.[80]

Inhibitori natrij-glukoza kotransporter 2 ne prestaju impresionirati u području bubrežnih bolesti. Nakon publiciranja rezultata važnih istraživanja *CREDENCE* i *DAPA-CKD*[81] u 2021., studija *SCORED*[82] koje je obuhvatila bolesnike oboljele od dijabetesa tipa 2 i kronične bubrežne bolesti, uz uporabu sotagliflozina ili placeba, pokazala je smanjenje primarnog ishoda (KV smrtnost ili događaji vezani za HF) za 37 % (HR: 0,74; 95 % CI: 0,63 –0,88: P <0,001). No sotagliflozin je bio pove-

First, besides the striking effects on hard endpoints, it is more and more recognized that functional status and symptoms are important to patients with HFrEF.[67] Both in DAPA-HF and EMPEROR-Reduced, these were improved,[68,69], although a smaller dedicated trial with empagliflozin did not improve functional status.[70] Further, a series of subanalyses showed no interaction of SGLT2 inhibitors with common HF drugs, such as MRAs, and most importantly, also not with sacubitril/valsartan.[71,72] Furthermore, the equal effects of the drugs were ascertained by analysing the effects across countries and ethnicities.[73] Another striking observation was that dapagliflozin was associated with a lower incidence of new-onset diabetes.[74] Collectively, to date, we have not seen any analysis suggesting a differential or lesser effect of SGLT2 inhibitors in HFrEF. We therefore must start to learn how to employ these drugs practically.[52,75]

Different from HFrEF, the efficacy of SGLT2 inhibitors in HFpEF remained to be proven. However, the EMPEROR-Preserved study presented during ESC 2021 demonstrated that empagliflozin reduced the primary combined endpoint of CV death and HF hospitalization in almost 6000 patients with HFpEF (**Figure 3**). These data are extremely important and provide hope for millions of HFpEF patients for whom there were no evidence-based therapies. Over a median follow-up of 26 months, the primary outcome event occurred in 13.8% of the patients in the empagliflozin group and in 17.1% in the placebo group [hazard ratio (HR): 0.79; 95% confidence interval (CI): 0.69–0.90; P,0.001]. Empagliflozin was very effective in reducing HF hospitalization, but all-cause mortality was not reduced. The effects of empagliflozin were consistent in patients with or without diabetes.[76,77] Shortly, the result of the second mortality trial in HFpEF with the SGLT2 inhibitor dapagliflozin, DELIVER, will be presented.[78]

Sodium–glucose co-transporter 2 inhibitors were also evaluated in patients with acute HF or immediately after acutely decompensated HF. The SOLOIST trial,[79] with the mixed SGLT 1/2 inhibitor sotagliflozin, enrolled 1244 patients with T2DM and recent worsening HF and showed a beneficial effect of the study drug, initiated before or shortly after discharge, with regard to a significantly lower total number of CV deaths and HF hospitalizations and urgent visits for HF. The ongoing EMPULSE trial will provide more data in the acute HF arena.[80]

Sodium–glucose co-transporter 2 inhibitors do not stop to amaze us in renal disease. After the publication of the hallmark trials CREDENCE and DAPA-CKD,[81] in 2021, the SCORED trial[82] came out, demonstrating in patients with T2DM and chronic kidney disease, allocated to sotagliflozin or placebo, a reduction of 37% in the primary endpoint of CV death and HF events (HR: 0.74; 95% CI: 0.63–0.88; P,0.001). However, sotagliflozin was associated with adverse events such as diarrhoea, genital mycotic infections, volume depletion, and diabetic ketoacidosis.

FIGURE 3. Please see Figure 3 in the original article.

zan s neželjenim učincima kao što su dijareja, mikotične infekcije genitalnog područja, deplecija volumena i dijabetična ketoacidoza.

ANTAGONISTI MINERALOKORTIKOIDNIH RECEPTORA (FIDELIO, FIGARO, HOMAGE)

Antagonosti mineralokortikoidnih receptora prva su linija terapije u HFrEF-u i mogu se razmatrati i u HFmrEF-u.[3] Finerenon, novi nesteroidni MRA, razlikuje se od steroidnih MRA s obzirom na distribuciju u tkivima, MR vezanje, kofaktore i ekspresiju gena.[83] U istraživanju *FIDELIO-DKD* finerenon je poboljšao KV i bubrežne ishode u bolesnika s kroničnim zatajenjem bubrega i tipom 2 dijabetesa s obzirom na bazalni status HF-a (G. Filippatos, 2021, rad poslan za publiciranje). U istraživanju *FIGARO-DKD* finerenon je smanjio primarni zajednički ishod (KV smrtnost, nefatalni infarkt miokarda, nefatalni moždani udar, hospitalizacije zbog HF-a), uz dobrobit primarno vezanu za nižu učestalost hospitalizacije zbog HF-a.[84] U bolesnika s visokim rizikom ili s KBS-om uz povišene vrijednosti natrijuretskih peptida, obuhvaćenih istraživanjem *HOMAGE*, nisu pod utjecajem liječenja spironolaktonom nađene interakcije početnoga serumskog galektina-3, kao ni promjene u prokolagen kolagen biomarkerima. Vrijednosti arterijskoga tlaka i NT-proBNP-a bile su primjenom spironolaktona snižene.[85]

AKTIVATORI SOLUBILNE GUANILAT CIKLAZE (VICTORIA)

Vericiguat, novi aktivator solubilne guanilat ciklaze, u subanalizi istraživanja *VICTORIA* nije smanjio pojavnost novonastale fibrilacije atrija. Postojeća fibrilacija atrija nije utjecala na povoljan učinak vericiguata u smislu primarnoga zajedničkog ishoda (vrijeme do KV smrtnosti ili prve hospitalizacije zbog HF-a) ili njegovih komponenti.[86] Povoljan učinak vericiguata bio je postojan kroz cijeli spektar bubrežne funkcije.[87]

AKTIVATORI SRČANOG MIOZINA

Substudija istraživanja *GALACTIC-HF* s miozin aktivatorom omecamtiv mecarbilom u bolesnika s HFrEF-om otkrila je da lijek smanjuje primarni ishod (hospitalizacije zbog HF-a i KV smrtnost) za 17 % u najnižoj kvartili (EF ≤22 %), ali nije registrirana dobrobit u najvišoj kvartili (EF ≥33 %).[88]

ŽELJEZOVA KARBOKSIMALTOZA (AFFIRM-AHF, IRON-CRT)

Nedostatak željeza povezan je s lošijim ishodima u bolesnika s HF-om. Istraživanje *AFFIRM-AHF* pokazalo je da u bolesnika s LVEF-om <50 % i nedostatkom željeza nakon hospitalizacije zbog akutnog HF-a, intravenska primjena željezove karboksimaltoze nije samo smanjila hospitalizacije zbog HF-a nego je rezultirala i u značajnim učincima na kvalitetu života.[89] U bolesnika s HFrEF-om (LVEF <45 %) i nedostatkom željeza, nakon resinkronizacijske terapije (istraživanje *IRON-CRT*), intravenska primjena željezove karboksimaltoze poboljšava strukturu i funkciju srca, kao i kvalitetu života.[90]

Nedostatak željeza također pridonosi rezistenciji na endogeni eritropoetin, što je važan razlog anemije u HF-u.[91]

OSTALO

U malom kliničkom istraživanju primjena lijeka CDR132L (oligonukleotidni lijek usmjeren protiv miR-132) dobro se tolerirala, pokazujući povezanost s poboljšanjem funkcije srca u bolesnika s HF-om.[92-94]

MINERALOCORTICOID RECEPTOR ANTAGONISTS (FIDELIO, FIGARO, HOMAGE)

Mineralocorticoid receptor antagonists are first-line therapies for HFrEF and may also be considered in HFmrEF.[3] Novel nonsteroidal MRA such as finerenone differ from steroidal MRA regarding tissue distribution, MR binding, recruitment of cofactors, and downstream gene expression.[83] In FIDELIO-DKD, finerenone improved CV and kidney outcomes in patients with chronic kidney disease and T2D regardless of baseline HF status (G. Filippatos, 2021, submitted for publication). In FIGARO-DKD, finerenone reduced the primary composite endpoint of death from CV causes, non-fatal myocardial infarction, non-fatal stroke, or HF hospitalization with the benefit driven primarily by a lower incidence of HF hospitalization.[84] In HOMAGE, in patients with, or at high risk for, coronary disease and raised NP levels, no interaction between baseline serum galectin-3 and changes in procollagen collagen biomarkers induced by spironolactone treatment was observed. However, blood pressure and NT-proBNP were reduced by spironolactone.[85]

ACTIVATORS OF SOLUBLE GUANYLATE CYCLASE (VICTORIA)

The novel activator of soluble guanylate cyclase, vericiguat, in a subanalysis of the VICTORIA trial, did not reduce new-onset atrial fibrillation. However, pre-existing atrial fibrillation did not affect the beneficial effect of vericiguat on the primary composite outcome (time to CV death or first HF hospitalization) or its components.[86] Similarly, beneficial effects of vericiguat were consistent across the full range of renal function.[87]

CARDIAC MYOSIN ACTIVATORS

A substudy of the pivotal trial of the myosin activator omecamtiv mecarbil (GALACTIC-HF) in patients with HFrEF found that the drug reduced the primary endpoint of HF hospitalization and CV death more as EF declined with a 17% decrease in the lowest quartile (EF≤22%) and no benefit in the highest quartile (EF≥33%).[88]

FERRIC CARBOXYMALTOSE (AFFIRM-AHF, IRON-CRT)

Iron deficiency is related to worse outcomes in HF. The AFFIRM-AHF study demonstrated that in patients with LVEF ,50% and iron deficiency after a hospitalization for acute HF, i.v. treatment with ferric carboxymaltose did not only reduce HF hospitalizations but also results in clinically meaningful beneficial effects on quality of life.[89] In HFrEF patients with iron deficiency and a persistently reduced LVEF ,45% after cardiac resynchronization therapy (IRON-CRT) study, i.v. ferric carboxymaltose FCM improved cardiac structure and function, as well as quality of life.[90]

Iron deficiency also contributes to resistance to endogenous erythropoietin, an important cause of anaemia in HF.[91]

OTHERS

In a small clinical trial, CDR132L, an antisense oligonucleotide drug directed against miR-132 was well tolerated and seemed to be associated with cardiac functional improvement in HF patients.[92–94]

In 50 patients with idiopathic chronic DCM and parvovirus B19 persistence, i.v. immunoglobulin therapy did not signifi-

U 50 bolesnika s idiopatskom kroničnom dilatativnom kardiomiopatijom i prisutnošću parvovirusa B19 intravenska imunoglobulinska terapija nije znatno poboljšala funkciju lijeve klijetke ili funkcionalni kapacitet uz standardnu medikamentnu terapiju.[95]

Uređaji i intervencijska terapija

RESINKRONIZACIJSKO LIJEČENJE

U bolesnika s HF-om, s fibrilacijom atrija i uskim QRS kompleksom, smrtnost i hospitalizacije zbog HF-a smanjuju se primjenom ablacije i resinkronizacijske terapije (CRT) u usporedbi sa (samo) farmakološkom terapijom. Ovakav povoljan učinak sličan je u bolesnika s LVEF-om ≤35 % i u onih s >35 %.[96] Smjernice za terapiju CRT-om nedavno su objavljene, kao i savjeti za optimalnu primjenu.[97,98] Kontroverze o tome dovodi li dodavanje ICD-a na CRT terapiju do dobrobiti u smislu smanjivanja smrtnosti (posebice u neishemijskom HF-u), nastavljaju se i dalje.[99]

PERKUTANA INTERVENCIJA NA MITRALNOM ZALISTKU

Američke Smjernice za valvularne bolesti, kao i Smjernice ESC-a iz 2021., preporuke za transkatetersku intervenciju na mitralnom zalistku (TEER) za sekundarnu (funkcionalnu) mitralnu regurgitaciju (SMR) dovele su na razinu preporuke II. A za bolesnike koji su zadovoljili kriterije iz *COAPT* istraživanja.[100,101] Zajednički je stav eksperata ESC-a da podržavaju ove preporuke.[102] Trogodišnji rezultati istraživanja *COAPT* prikazali su dobrobit od primjene TEER-a.[103] Važna sekundarna analiza tog istraživanja pokazuje da se rezidualni stupanj mitralne insuficijencije 3 – 4+ može snažno povezati s lošijim ishodima u skupini liječenoj TEER-om i onoj na medikamentnoj terapiji.[104] U bolesnika s fibrilacijom atrija TEER je bio povezan s nižim rizikom od moždanog udara.[105] U subgrupi *MITRA-FR* koja oponaša bolesnike iz istraživanja *COAPT*, nije dokazana dobrobit od primjene TEER-a, dok u subgrupi iz *COAPT-a* koja oponaša bolesnike iz *MITRA-FR* nije zabilježeno smanjenje hospitalizacije zbog HF-a.[106,107]

IMPLANTABILNI HEMODINAMSKI MONITORI

U istraživanju *GUIDE-HF* evaluirano je hemodinamski vođeno monitoriranje kako bi se smanjile hospitalizacije zbog HF-a, kao i smrtnost u bolesnika s II. do IV. stupnjem prema NYHA klasifikaciji uz sve vrijednosti ejekcijske frakcije. Ukupna je analiza bila negativna, no, kada se pribroji liječenje bolesti COVID-19, dolazi do znatnog smanjivanja hospitalizacije zbog HF-a u bolesnika s II. – III. stupnjem prema NYHA, bilo s prethodnom hospitalizacijom zbog HF-a ili povišenim razinama natrijuretskog peptida.[108]

Specifično liječenje

TELEMEDICINA I DALJINSKO PRAĆENJE

U preglednome članku Bekfani *i sur.* evaluirali su potrebe liječenja bolesnika s HF-om kako bi monitoriranje na daljinu moglo pridonijeti budućim rješenjima te su prikazali aktualne i nove tehnologije daljinskog monitoriranja.[109] Velika raznolikost inovativne tehnologije za daljinsko monitoriranje i algoritme uključuje: samotestiranje bolesnika, nosive uređaje, tehnologiju integriranu u klinički indicirane terapijske

cantly improve LV systolic function or functional capacity beyond standard medical therapy.[95]

Device and interventional therapies

CARDIAC RESYNCHRONIZATION THERAPY

In patients with HF, atrial fibrillation and a narrow QRS mortality and HF hospitalizations were reduced by atrioventricular junctional ablation and cardiac resynchronization therapy (CRT) compared with pharmacological treatment alone; this beneficial effect was similar in patients with LVEF≤35% and .35%.[96] Guidelines for CRT and suggestions for optimized implementation have recently been published.[97,98] The controversy about whether adding an ICD to CRT provide additional mortality benefit, especially in non-ischaemic HF continues.[99]

PERCUTANEOUS MITRAL VALVE REPAIR

The US Valvular Disease Guidelines as well as the 2021 ESC Guidelines on valvular heart disease recently upgraded the recommendation for transcatheter mitral valve repair (TEER) for secondary (functional) mitral regurgitation (SMR) to a IIA recommendation for patients who meet COAPTcriteria.[100,101] Ajoint position statement from the ESC supports this recommendation.[102] The 3-year results of the COAPT trial demonstrate the ongoing benefit of TEER.[103] An important secondary analysis from COAPT demonstrates that residual 3–4+ SMR is the strongest risk factor for poor outcomes in both the TEER group and in the medical therapy group.[104] In patients with atrial fibrillation, TEER was associated with a lower risk of stroke.[105] Subgroups of MITRA-FR mimicking COAPT patients did not show a benefit of TEER, although a subgroup of COAPT mimicking MITRA-FR patients did show a benefit in HF hospitalizations.[106,107]

IMPLANTABLE HAEMODYNAMIC MONITORS

The GUIDE-HF trial evaluated haemodynamic guided management to reduce HF hospitalizations and mortality in patients with NYHA II-IV and all ejection fractions. The overall analysis was negative but when COVID-19 was accounted for there was a significant reduction in HF hospitalization in NYHA II-III patients with either a previous HF hospitalization or elevated NPs.[108]

Specific management

TELEMEDICINE AND REMOTE MONITORING

In a comprehensive review, Bekfani and colleagues discuss unmet needs in the management of patients with HF, how remote monitoring might contribute to future solutions and provide an overview of current and novel remote monitoring technologies.[109] A great variety of innovative remote monitoring technologies and algorithms including patient self-managed testing, wearable devices, technologies integrated into clinically indicated therapeutic devices, such as pacemakers and defibrillators, and landmark clinical trials of remote monitoring were reviewed.

uređaje (elektrostimulatori, defibrilatori) i druge istraživačke kliničke studije daljinskog telemonitoriranja.

REHABILITACIJA

U ekspertnom dokumentu o kardiološkoj rehabilitaciji bolesnika s HF-om Bozkurt *i sur.*[110] iznijeli su opći pregled učinkovitosti i sigurnosti vježbanja i kardiološke rehabilitacije u bolesnika s HFrEF-om i HFpEF-om, kao i preporuke za praktičan pristup. Istraživali su razloge i rješenja suboptimalne primjene kardiološke rehabilitacije u bolesnika s HF-om. U istraživanju *REHAB-HF* na različitim populacijama bolesnika starije dobi (koji su bili hospitalizirati zbog akutnog HF-a) primjena rane, postupne, progresivne rehabilitacijske intervencije koja uključuje multiple fizičke funkcionalne domene donosi veće poboljšanje tjelesne funkcije nego uobičajeno liječenje. To važno istraživanje pokazalo je sigurnost i učinkovitost započinjanja progresivne rehabilitacije koju bi trebalo započeti za vrijeme i rano nakon hospitalizacije u bolesnika s HF-om, neovisno o vrijednostima LVEF-a.[111]

REHABILITATION

In an Expert Panel consensus document on Cardiac Rehabilitation for Patients with Heart Failure, Bozkurt et al.[110] provide an overview of efficacy and safety evidence of exercise training and cardiac rehabilitation in HFrEF and HFpEF, recommendations on practical approaches to exercise training and cardiac rehabilitation in patients with HF and examine the reasons and solutions for underutilization of cardiac rehabilitation in HF patients. In the REHAB-HF trial, in a diverse population of older patients who were hospitalized for acute decompensated HF, an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical function domains resulted in greater improvement in physical function than usual care. This is an important study demonstrating the safety and efficacy of initiation of progressive rehabilitation initiated during and early posthospitalization in HF patients regardless of LVEF.[111]

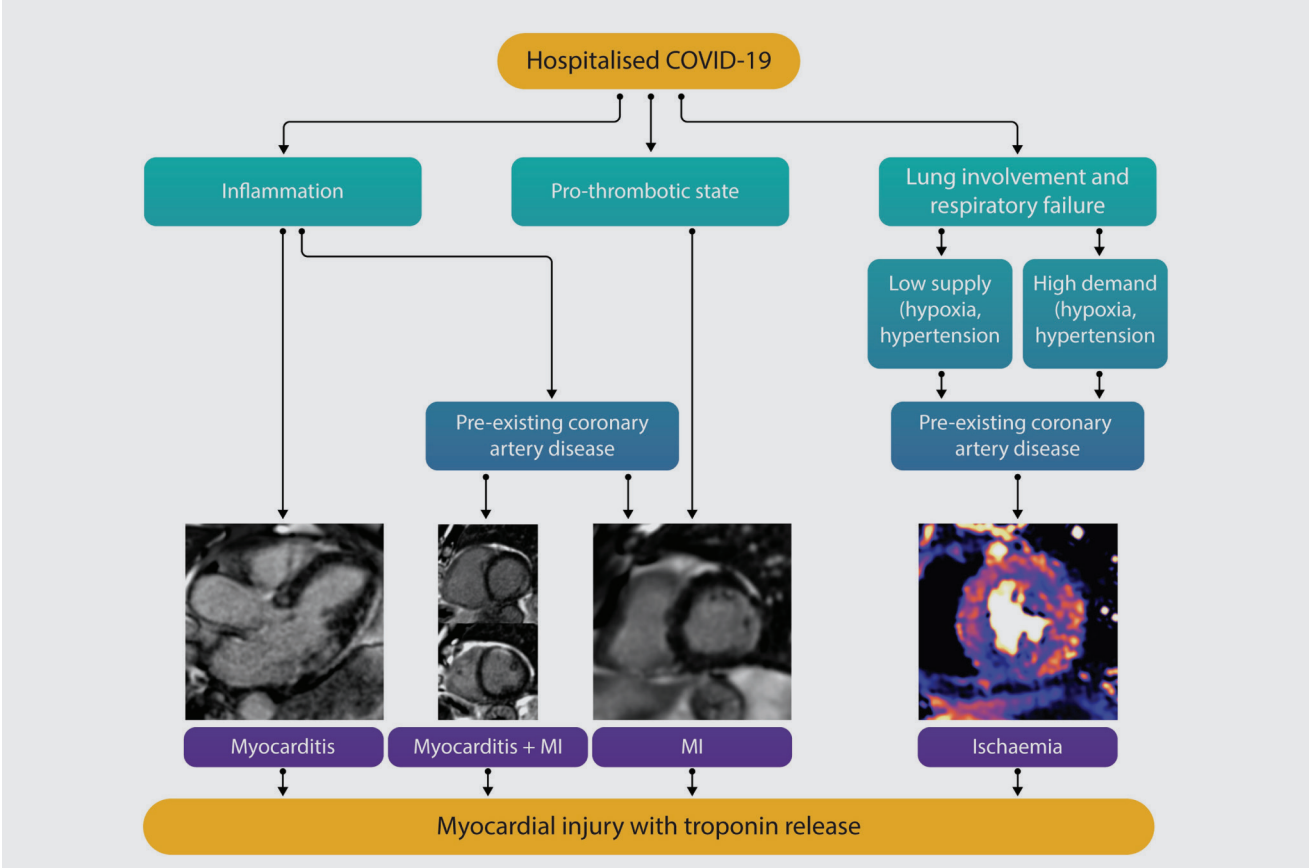

FIGURE 4. Myocardial injury in recovered COVID-19 patients assessed by cardiovascular magnetic resonance. Myocarditis-like injury can be encountered, with limited extent and minimal functional consequence. Reprinted with permission from Kotecha *et al.*[127 6] (from Bauersachs J, de Boer RA, Lindenfeld J, Bozkurt B. The year in cardiovascular medicine 2021: heart failure and cardiomyopathies. Eur Heart J. 2022 Feb 3;43(5):367-376. doi: 10.1093/eurheartj/ehab887, by permission of OUP on behalf of the ESC).

Zatajivanje srca tijekom pandemije bolesti COVID-19

Pojavnost akutnog HF-a bilježi se kao komplikacija u 2 %, a ozljeda miokarda u 10 % bolesnika hospitaliziranih zbog bolesti COVID-19.[112] Povećane početne vrijednosti NT-proBNP-a povezane su s većom smrtnosti[113], a povećanje kardiološke miocitno-specifične microRNAs, u kritično bolesnih bolesnika s COVID-om 19, upućuje na kardiološku problematiku.[114] Snižavanje učestalosti prijema bolesnika s HF-om[115] i visoka izvanbolnička smrtnost[116] tijekom „lockdowna" prepoznati su kao alarmantni podatak, a odraz je nemogućnosti pristupa medicinskoj skrbi bolesnika s HF-om. Randomizirana su istraživanja pokazala sigurnost nastavka primjene ACEi ili ARB-a, u bolesnika hospitaliziranih zbog bolesti COVID-19.[117-119] Primjena dapagliflozina nije znatno smanjila disfunkciju organa ili smrt u bolesnika s COVID-om 19, a tolerancija lijeka bila je dobra (istraživanje *DARE-19*).[120] Miokarditis je rijetka komplikacija COVID-19 mRNA vakcinacije, posebno u mlađih muškaraca.[121] Omjer dobrobiti i rizika od cijepljenja protiv bolesti COVID-19 povoljan je u svim dobnim i spolnim skupinama, a gotovo svi bolesnici s miokarditisom imaju rezoluciju svih simptoma i znakova bolesti.[121] Dugotrajne komplikacije SARS-CoV-2 infekcije uključuju perzistiranje sinusne tahikardije, posturalni ortostatski tahikardija sindrom, atrijske aritmije i kardiomiopatiju.[122] U sportaša koji su se oporavili od bolesti COVID-19 nekoliko istraživanja magnetnom rezonancijom upozorilo je na promjenjivi stupanj kardioloških abnormalnosti koje su govorile u prilog dijagnozi miokarditisa.[123,124] Kada probir troponinom, EKG-om, ehokardiografijom i dodatno magnetnom rezonancijom i/ili stresnom ehokardiografijom pronađe abnormalnosti, samo 0,6 % sportaša ima ograničenje povratka na sportske aktivnosti, a nijedan nema kardiološke događaje.[125] Iako je ozljeda miokarda česta u bolesti COVID-19, a SARS-CoV-2 RNA može se detektirati u srcu, miokarditis je rijetka patološka dijagnoza i pojavljuje se u 4,5 % visokoselekcioniranih slučajeva koji su bili podvrgnuti obdukciji ili biopsiji miokarda.[126] Tijekom oporavka nakon teškog oblika bolesti COVID-19 s povišenim troponinom, može se magnentom rezonancijom detektirati ozljeda koja nalikuje na miokarditis, no uz ograničenu proširenost i minimalne funkcionalne posljedice (**slika 4**).[127]

Heart failure during the COVID-19 pandemic

Incident acute HF was recognized as a complication in 2%, and myocardial injury in 10% of all patients hospitalized with COVID-19.[112] Elevated admission NT-proBNP levels were associated with higher mortality,[113] and cardiac myocyte-specific microRNAs were upregulated in critically ill COVID-19 patients indicating cardiac involvement.[114] Declining overall admission rates for HF[115] and higher out-of-hospital mortality rates[116] during lockdown were recognized as alarming issues, reflecting lack of access to care among patients with established HF. Randomized trials demonstrated the safety of continuation of ACE inhibitors or ARB among patients hospitalized with COVID-19.[117–119] Dapagliflozin treatment did not significantly reduce organ dysfunction or death, but was well tolerated in patients hospitalized with COVID-19 (DARE-19 trial).[120] Myocarditis emerged as a rare complication of COVID-19 mRNA vaccinations, especially in young men.[121] Benefit–risk assessment for COVID-19 vaccination was favourable for all age and sex groups; and almost all patients with myocarditis had resolution of symptoms and signs.[121] Long-term complications of SARS-CoV-2 infection include persistent sinus tachycardia, postural orthostatic tachycardia syndrome, atrial arrhythmia, and cardiomyopathy.[122] Among athletes recovering from COVID-19, several CMR studies reported varying rates and degrees of cardiac abnormalities suggestive of myocarditis. [123,124] Screening by troponin, ECG, echocardiography, and additional CMR and/or stress echocardiography if abnormal, resulted in only 0.6% of the athletes being restricted to return to sports, and none had cardiac events.[125] Though myocardial injury is common in COVID-19, and SARS-CoV-2 RNA can be detected in the heart, myocarditis is an uncommon pathologic diagnosis occurring in 4.5% of highly selected cases undergoing autopsy or endomyocardial biopsy.[126] During convalescence after severe COVID-19 infection with troponin elevation, myocarditis-like injury can be detected by CMR, however, with limited extent and minimal functional consequence (**Figure 4**).[127]

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