Godina 2019. u kardiologiji: zatajivanje srca

The year in cardiology: heart failure
The year in cardiology 2019

John G.F. Cleland[1,2,3]*, **Alexander R. Lyon**[2,4], **Theresa McDonagh**[5,6], **John J.V. McMurray**[3]

[1]Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow, Glasgow, United Kingdom
[2]National Heart & Lung Institute, Imperial College, London, United Kingdom
[3]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom
[4]Royal Brompton Hospital, London, United Kingdom
[5]King's College Hospital, London, United Kingdom
[6]King's College London, London, United Kingdom

RECEIVED:
January 9, 2020
ACCEPTED:
January 21, 2020

CITATION: Cardiol Croat. 2020;15(7-8):167-88. | https://doi.org/10.15836/ccar2020.167

***ADDRESS FOR CORRESPONDENCE**: John G.F. Cleland, Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow, Glasgow G12 8QQ, United Kingdom. / Phone: +44-141-330-5299 / E-mail: john.cleland@glasgow.ac.uk

ORCID: John G.F. Cleland, https://orcid.org/0000-0002-1471-7016

TO CITE THIS ARTICLE: Cleland JGF, Lyon AR, McDonagh T, McMurray JJV. The year in cardiology: heart failure. Cardiol Croat. 2020;15(7-8):167-88. | https://doi.org/10.15836/ccar2020.167

TO LINK TO THIS ARTICLE: https://doi.org/10.15836/ccar2020.167

Reproduced from: Cleland JGF, Lyon AR, McDonagh T, McMurray JJV. The year in cardiology: heart failure. Eur Heart J. 2020 Mar 21;41(12):1232-1248. https://doi.org/10.1093/eurheartj/ehz949, by permission of Oxford University Press on behalf of the European Society of Cardiology.

Uvod

Protekla nam je godina donijela mnogo novih koncepata i obilje podataka o naravi, liječenju i ishodima zatajivanja srca (HF). Tempo se promjena ubrzava. Očekuje nas zanimljivo novo desetljeće istraživanja. Prognoza kardiovaskularnih bolesti u velikoj je mjeri određena sposobnošću odgađanja ili prevencije razvoja ili progresije HF-a.[1] U skladu s tim, pozornost se usmjeruje prema ranijem otkrivanju i interveniranju pri HF-u. Bolesnici s tipom 2 šećerne bolesti (T2DM)[2] ili koronarnom bolesti srca (CAD)[3] imaju relativno dobru prognozu ako nisu povećane vrijednosti natriuretskih peptida, što upućuje na značajnu srčanu ili bubrežnu disfunkciju. Prihvaćanjem jednostavne „univerzalne definicije" HF-a baziranog na vrijednosti natriuretskog peptida omogućit će se rana dijagnoza i liječenje, ali će dovesti i do golemog porasta prevalencije te opterećenja zdravstvenih službi.[4] Moramo se pripremiti na neminovan udar.

Preamble

The past year has brought many new concepts and an abundance of new data on the nature, management, and outcome of heart failure. The pace of change is accelerating. We look forward to an exciting new decade of research. The prognosis of cardiovascular disease is determined to a large extent by the ability to delay or prevent the development and progression of heart failure.[1] Accordingly, attention is shifting to earlier diagnosis of and intervention for heart failure. Patients with type-2 diabetes mellitus (T2DM)[2] or coronary artery disease (CAD)[3] have a relatively good prognosis unless plasma concentrations of natriuretic peptides are increased, indicating important cardiac or renal dysfunction. Adoption of a simple 'Universal Definition' of heart failure based on natriuretic peptides would facilitate early diagnosis and treatment but lead to an enormous increase in its prevalence and demand upon medical services.[4] We need to prepare for the impending shock.

Epidemiologija i prevencija

U kardiologiji se izraz prevencija često uporabljuje u značenju odgađanja nastupa bolesti. Pogreška pri razumijevanju razlike između prevencije i odgađanja dovodi do problema u planiranju budućih potreba i troškova zdravstvenog sustava. Stariji ljudi imaju više komorbiditeta koji liječenje čine zahtjevnim, ali se otvara više mogućnosti za intervencije; posljedično, potrebno je više vremena i sredstava za dobro zbrinjavanje osoba starije životne dobi.

Englesko istraživanje pokazuje da se medijan dobi nastupa HF-a povisio na oko 80 godina, što je u skladu s poboljšanjem liječenja arterijske hipertenzije i drugih aterosklerotskih čimbenika rizika te boljeg liječenja infarkta miokarda.[5] Nažalost, podatci o istisnoj frakciji lijeve klijetke (LVEF) nisu bili dostupni u spomenutom istraživanju. Analiza engleskih dijagnostičkih algoritama u primarnoj praksi upućuje na to da se bitni postupci često se ne provedu.[6-8] Žurno nam trebaju slični podatci iz ostalih zemalja. Nedavno je objavljeno nekoliko velikih epidemioloških istraživanja[9,10] i analiza velikih studija[11,12] koje nam omogućuju međunarodnu usporedbu demografskih, etioloških i faktora liječenja HF-a.

Antagonisti mineralokortikosteroidnih receptora (MRAs) efikasni su antihipertenzivni lijekovi koji isto tako poboljšavaju prognozu bolesnika s HF-om sa sniženom istisnom frakcijom (HFrEF) te moguće i očuvanom (HFpEF) LVEF.[13] U tijeku su istraživanja imaju li MRAs specifične učinke na smanjenje ostalih potencijalnih pokretača progresije HF-a kao što su upala ili fibroza.[14,15]

Genska sklonost većoj količini masnoga tkiva bila je povezana s većim rizikom od razvoja HF-a u analizi 367 703 ispitanika iz *UK Biobank*.[16] Međutim, incidencija HF-a bila je samo 1% (4803 bolesnika), dijagnostički kriteriji nisu bili snažni i povećanje rizika bilo je skromno (odds ratio 1,22; 95% CI 1,06 – 1,41). Daljnje analize na spomenutoj skupini pokazale su jaku korelaciju između kardiorespiratornog vježbanja, jačine stiska šake i buduće incidencije HF-a.[17] Studija na 4403 bolesnika predviđena za barijatrijsku kirurgiju u Švedskoj i praćenih 22 godine pokazala je da se u 188 (9 %) od 2003 iz skupine operiranih ispitanika (25 – 35 kg gubitka tjelesne težine: indeks tjelesne mase godinu dana nakon zahvata 32 kg/m^2) razvio HF prema 266 (13 %) iz skupine od 2030 koji nisu bili operativno liječeni (ITM nakon jedne godine praćenja 40 kg/m^2).[18] Iako ovi podatci upućuju na povezanost između pretilosti i rizika od razvoja HF-a, moguće je da pretilost samo provocira slične simptome. Kada je već nastupilo HF, pretilost je povezana s manjim mortalitetom, ali to može više biti odraz ranije dijagnoze nego protektivnog učinka.[19] Potrebne su randomizirane kontrolirane studije (RCTs) učinkovitih intervencija kod pretilosti da bi se dokazalo poboljšava li gubitak težine simptome (vjerojatno) i kliničke ishode (manje uvjerljivo).

U izvještaju istraživanja *Atherosclerosis Risk in Communities* potvrđena je povezanost između epidemije gripe i hospitalizacija zbog HF-a, što pojačava preporuku u smjernicama za cijepljenje[20], a randomizirana je studija u tijeku.[21] Produljeno praćenje (medijan 18,9 godina) u studiji *Women s Health Initiative Hormone Therapy* kod 27 347 žena randomiziranih na različite hormonske nadomjesne terapije nije pokazalo da imaju utjecaja na incidenciju HFrEF ili HFpEF.[22]

Studija *ISCHAEMIA* (prikazana na kongresu Američkoga kardiološkog društva AHA 2019.) uspoređivala je strategiju rane koronarne revaskularizacije, uglavnom perkutane, sa

Epidemiology and prevention

In cardiology, the term prevention is often used to mean delaying the onset of disease; in other words, procrastination. Failure to appreciate the difference between prevention and procrastination leads to problems in projecting future healthcare needs and costs. Older people have more co-morbid conditions that complicate management but may also offer more opportunities for intervention; consequently, more time and resources are required to manage older patients well.

A detailed report on heart failure in the UK shows that the median age of onset has risen to about 80 years, consistent with improvements in the treatment of hypertension and other risk factors for atherosclerosis and better management of myocardial infarction.[5] Unfortunately, data on left ventricular ejection fraction (LVEF) were not available for this report. Analyses of the diagnostic pathway in primary care in the UK suggest that key investigations are often not done.[6-8] Similar data from other countries are urgently required. Several large epidemiological surveys[9,10] and analyses of large trials[11,12] have recently been published that allow the demographics, aetiology, and management of heart failure to be compared internationally.

Mineralocorticoid receptor antagonists (MRAs) are effective anti-hypertensive agents that also improve the prognosis of patients with heart failure and a reduced (HFrEF) and possibly preserved (HFpEF) LVEF.[13] Whether MRAs have specific effects on reducing other potential drivers of the progression to heart failure such as inflammation and fibrosis is currently under investigation.[14,15]

Genetic propensity to greater body fat was associated with the risk of developing heart failure in an analysis on 367 703 UK Biobank participants.[16] However, the incidence of heart failure was only 1% (4803 patients), the diagnostic criteria were not robust, and the increase in risk was modest (odds ratio 1.22; 95% CI 1.06–1.41). Further analyses on this population showed a strong relationship between cardio-respiratory fitness and grip strength and future incidence of heart failure.[17] A study of 4403 people considered for bariatric surgery in Sweden and followed for 22 years, found that 188 (9%) of the 2003 who had surgery (25–35 kg weight loss; BMI 1 year after surgery 32 kg/m^2) developed heart failure compared with 266 (13%) of 2030 who did not (BMI after 1 year observation 40 kg/m^2).[18] Although these data suggest links between obesity and the risk of developing heart failure, it is possible that obesity just provokes similar symptoms. Once heart failure has developed, obesity is associated with a lower mortality, but this may also reflect earlier diagnosis rather than a protective effect.[19] Randomized controlled trials (RCTs) of effective interventions for obesity are required to demonstrate whether weight loss improves symptoms (likely) and clinical outcomes (less certain).

A report from 'the Atherosclerosis Risk in Communities' (ARIC) study confirmed the association between influenza epidemics and hospitalizations for heart failure, reinforcing guideline-recommendations for vaccination[20]; an RCT is underway.[21] Extended follow-up (median 18.9 years) of the Women's Health Initiative Hormone Therapy trials, which randomized 27 347 women to various hormone replacement regimens, showed that they had no effect on the incidence of HFrEF or pEF.[22]

The ISCHEMIA trial (presented at the American Heart Association 2019) compared strategies of early coronary revascularization, predominantly percutaneous, with conservative

strategijom konzervativnog liječenja stabilne CAD, neki od bolesnika imali su blage simptome HF-a i/ili sniženu LVEF. Revaskularizacija nije smanjila rizik od infarkta miokarda i smrti, ali je povećala rizik od moždanog udara gotovo četiri puta i nije smanjila pojavu novonastalog HF-a u praćenju tijekom 4 godine.

Dijagnoza

Udruženje za zatajivanje srca Europskoga kardiološkog društva preporučila je novi bodovni sustav za dijagnozu HFpEF-a.[23] Čeka se potvrda njegove uporabljivosti u praksi.[24] Preferiraju se jednostavnije metode.[4]

Kongestija

Kongestija je temeljna promjena u HF-u.[25-27] Slikovne su metode dugo primjenjivane za prikazivanje dilatacije atrija i venskog sustava, što se može nazvati hemodinamskom kongestijom, a natriuretski su peptidi koristan biomarker za to.[25] U novije se vrijeme slikovni prikaz uporabljuje za utvrđivanje tekućine u tkivima (tkivna kongestija),[25,28-32] što može biti povezano s povišenim biomarkerom, (bio)-adrenomedulinom.[33] Slikovni prikaz i biomarkeri u kombinaciji osjetljivi su i specifični za otkrivanje zatajivanja srca, te su koristan pokazatelj stupnja kongestije, prognoze i potencijalnog terapijskog cilja prikazivanjem uspješnog liječenja. Slikovne metode ostaju metode izbora za određivanje uzroka HF-a. Ako je kongestija u središtu liječenja HF-a, tada bi bolji monitoring[34] i učinkovitija (diuretska) terapija (moguće acetazolamidom?[35]) trebali dovesti do boljih ishoda (**slika A** – *Take home figure*).

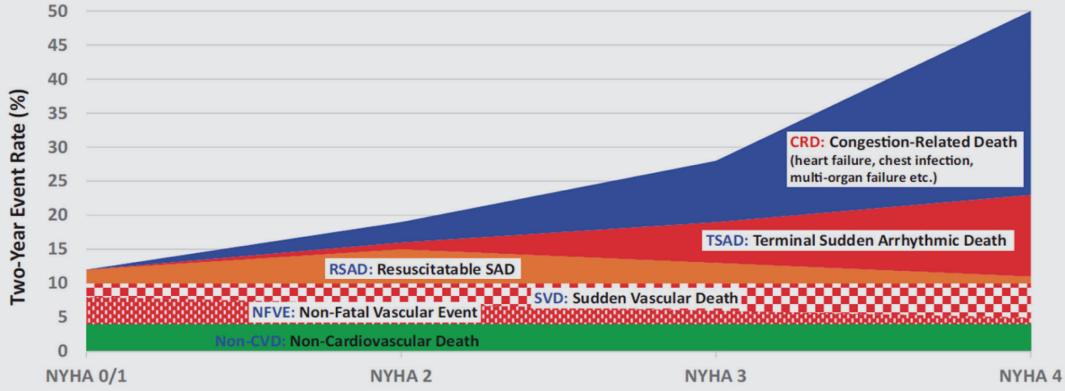
management for stable CAD, some of whom had mild symptoms of heart failure and/or a reduced LVEF. Revascularization did not reduce the risk of myocardial infarction or death but increased the risk of stroke almost four-fold and did not reduce new-onset heart failure over the following 4 years.

Diagnosis

The Heart Failure Association of the European Society of Cardiology has proposed a new scoring system for the diagnosis of HFpEF.[23] Its practical utility awaits confirmation.[24] Simpler approaches may be preferred.[4]

Congestion

Congestion lies at the heart of failure.[25–27] Imaging has long been used to identify dilation of the atria and venous system, which might be termed haemodynamic congestion, for which natriuretic peptides are a useful biomarker.[25] More recently imaging has been used to identify accumulation of fluid in tissues (tissue congestion),[25,28–32] which may be associated with increases in the biomarker, (bio)-adrenomedullin.[33] Imaging and biomarkers in combination are both sensitive and specific for detecting a failing heart, a useful guide to the severity of congestion and prognosis and a potential therapeutic target indicating successful management. Imaging remains the preferred method for identifying the cause of heart failure. If congestion is central to the management of heart failure, then better monitoring[34] and more effective (diuretic) interventions (perhaps acetazolamide?[35]) should improve outcome (**Figure A** – *Take home figure*).



	NYHA 0/1		NYHA 2		NYHA 3		NYHA 4	
	Absolute Rate	% of Events	Absolute Rate	% of Events	Absolute Rate	% of Events	Absolute Rate	% of Events
CRD	0%	0%	3%	16%	9%	32%	27%	54%
TSAD	<1%	<1%	1%	5%	6%	21%	12%	24%
RSAD	2%	17%	5%	26%	3%	11%	1%	2%
SVD	2%	17%	3%	16%	4%	14%	5%	10%
NFVE	4%	33%	3%	16%	2%	7%	1%	2%
Non-CVD	4%	33%	4%	21%	4%	14%	4%	8%

FIGURE A. *Take home figure:* Two-year cause-specific mortality and non-fatal vascular events for patients with cardiovascular disease according to New York Heart Association (NYHA) class. Numbers and proportions are a conceptual representation of absolute and relative risk and are not strictly evidence-based. Note that for patients in NYHA Class 4, interventions for sudden arrhythmic death may be ineffective or fail to lead to a meaningful prolongation of life because the patient is likely soon to die of worsening heart failure.

CRD, congestion-related death, otherwise called death due to worsening heart failure; NFVE, non-fatal vascular event (e.g. myocardial infarction and stroke; note that events are more likely to be suddenly fatal as heart failure progresses); non-CVD, non-cardiovascular death; RSAD, resuscitatable sudden arrhythmic death; SVD, sudden vascular death; TSAD, terminal (non-resuscitatable) sudden arrhythmic death. Reproduced with permission from ref.[29]

Životna dob i prognoza

Analiza velikih baza podataka primarne prakse upućuje na to da se kardiovaskularna (CV) prognoza novootkrivenih HF-a znatno poboljšala između godine 2002. i 2014. (hazard ratio (HR): 0,73; 95% CI 0,68 – 0,80) za bolesnike iznad i ispod dobi od 80 godina.[5] Međutim, u osoba u dobi >80 godina smanjenje smrtnosti od CV-a u cijelosti je nadoknađeno nekardiovaskularnom smrtnosti. Drugim riječima, liječenje je promijenilo način na koji stariji ljudi umiru, ali nije promijenilo ukupnu smrtnost (**slika 1**). Nažalost, podatci o LVEF-u nisu bili dostupni i velik je broj bolesnika mogao imati HFpEF pa stoga treba biti pažljiv pri pripisivanju redukcije smrtnosti od CV-a liječenju HF-a. Sustavni pregledi istraživanja i registara također potvrđuju da se poboljšala prognoza HF-a; važne odrednice ishoda bile su dob i doprinos kardiologije liječenju.[36] Nemoć koja se više smatra biološkom nego kronološkom mjerom starosti, mogla bi biti još snažniji prediktor invalidnosti i smrti.[37]

Age and prognosis

Analysis of a large primary care database suggested that the cardiovascular (CV) prognosis of new-onset heart failure improved substantially between 2002 and 2014 [hazard ratio (HR): 0.73; 95% CI 0.68–0.80] for patients above and below the age of 80 years.[5] However, in those aged >80 years, the fall in CV mortality was entirely offset by non-CV mortality. In other words, treatment changed the way that elderly patients died but not overall mortality (**Figure 1**). Unfortunately, information on LVEF was not available; many patients will have had HFpEF and, therefore, caution should be exercised in attributing the reduction in CV mortality to treatment of heart failure. A systematic review of survey and registry data also suggested that the prognosis of heart failure had improved; important determinants of outcome were age and cardiology input to management.[36] Frailty, which might be considered a biological rather than chronological measure of age, may be an even more powerful predictor of disability and death.[37]

FIGURE 1. Please see the original article (Eur Heart J. 2020 Mar 21;41(12):1232-1248.).

Preporuke smjernica za liječenje HFrEF-a nisu diskriminirajuće po dobi. Švedski registar zatajivanja srca pokazao je da je propisivanje ACE inhibitora i beta-blokatora za bolesnike s HFrEF-om u dobi >80 godina bilo povezano s manjim mortalitetom.[38,39] Međutim, opservacijske poveznice imaju mnoga druga objašnjenja osim samih terapijskih učinaka.[40] Metaanaliza individualno strukturiranih podataka iz triju randomiziranih istraživanja o MRA (*RALES, EMPHASIS i TOPCAT - Americas*)[13] pokazuje da MRA utječu sličnim smanjenjem na mortalitet (oko 25 %) u bolesnika s HFrEF-om mlađih i starijih od 75 godina, dok je povoljan učinak manje uvjerljiv za HFpEF.

Raznolikost fenotipa zatajivanja srca

„Precizna medicina", koja je bi isto tako trebala biti vrlo detaljna, zahtijeva klasifikaciju bolesnika koja nas informira o daljnjem liječenju. U onkologiji je fokus na analizi genskih promjena, lokaciji tumora i na proširenosti bolesti. Kod HF-a, multisistemskog poremećaja, sve je još kompleksnije.[41-47]

Trenutačna terapijski relevantna klasifikacija HF-a uključuje stupanj kongestije (temeljeno na simptomima, znakovima, krvnim biomarkerima i slikovnim metodama), CAD, frekvenciju srca, ritam i trajanje QRS-a, arterijski tlak, serumski kalij, bubrežnu funkciju, pokazatelje deficita željeza, mitralnu regurgitaciju, infitrativne bolesti miokarda (npr. amiloid) i fenotip klijetke.[41,48] Optimalno liječenje HF-a, uz vrlo rijetke iznimke, zahtijeva malu količinu informacija, ali to ipak dovodi do stvaranja tisuća podgrupa bolesnika i skupina koje bi mogle imati različite terapijske potrebe.[45,46] Broj podgrupa povećavat će se eksponencijalno s uvođenjem svakog novog oblika liječenja. Usprkos heterogenosti supstrata i mnogim

Guideline-recommendations for the treatment of HFrEF do not discriminate by age. The Swedish Heart Failure Registry found that prescription of ACE inhibitors or beta-blockers to patients with HFrEF aged >80 years was associated with a lower mortality.[38,39] However, observational associations have many explanations other than a therapeutic effect.[40] An individual patient-data meta-analysis of three RCTs of MRA (RALES, EMPHASIS, and TOPCAT-Americas)[13] suggested that MRAs exerted a similar reductions in mortality (by about 25%) for patients with HFrEF above and below age 75 years but benefit was less certain for HFpEF.

The diversity of heart failure phenotypes

Precision-medicine, which should also be accurate, requires patients to be classified in a way that informs management. For oncology, this has focused on the genetic cause, tumour location, and spread. For heart failure, a multi-system disorder, it is much more complex.[41–47]

Current, therapeutically relevant classifications of heart failure include the severity of congestion (based on symptoms, signs, blood biomarkers, and imaging), CAD, heart rate and rhythm and QRS duration, blood pressure, serum potassium, renal function, indices of iron deficiency, mitral regurgitation, infiltrative myocardial disease (e.g. amyloid), and ventricular phenotype.[41,48] Optimal management of heart failure, with a few rare exceptions, requires only a modest amount of information but this still creates many thousands of patient-subgroups or clusters that might have different therapeutic needs.[45,46] Such subgroups will increase exponentially with the introduction of each new class of treatment. Despite this heterogeneity of sub-

mogućim intervencijama, „precizna medicina" je u povojima za HF.

Jedna je terapijski relevantna klasifikacija HF-a po vrijednostima LVEF-a, surogatu dilatacije lijeve klijetke (LV). Prije 1980. godine oslikavanje funkcije srca bilo je dostupno samo u ekspertnim centrima. Za potvrdu dijagnoze HF-a kliničke studije više su se oslanjale na radiološku snimku prsišta nego na ehokardiogram. Uspjeh istraživanja kao što su *SOLVD, MERIT* i *CHARM*, koja su sva kao uključni kriterij imale sniženu LVEF, doveo je do prihvaćanja LVEF-a <40 % kao definiciju smjernica Europskog kardiološkog društva (ESC) za HFrEF.[49] Vrijednosti ≥40 % nazvane su HFpEF-om, uključujući bolesnike s umjereno ili blago sniženom (HFmrEF), normalnom (HFnEF) i moguće supranormalnom (HFsnEF) LVEF.[50] Analiza više od 350 000 sakupljenih standardiziranih ehokardiograma upućuje na to da se najniža vrijednost, ima li ili nema bolesnik dijagnozu HF-a, nalazi u rasponu 60 – 65 % i za žene i za muškarce. Zanimljivo je da LVEF >70 % povezana s istim rizikom kao i LVEF 30 – 40 % (**slika 2**).[50]

strate and wealth of interventions, precision-medicine is in its infancy in heart failure.

One therapeutically relevant classification of heart failure is by LVEF, a surrogate for left ventricular (LV) dilation. Prior to the 1980s, imaging of cardiac function was available only in expert centres. Clinical trials relied on the chest X-ray rather than the echocardiogram to support a diagnosis of heart failure. The success of trials such as SOLVD, MERIT, and CHARM, which all had a reduced LVEF as an inclusion criterion, led to the adoption of LVEF <40% as the European Society of Cardiology (ESC) Guideline definition for HFrEF.[49] Values ≥40% were termed HFpEF, comprising patients with a mid-range or mildly-reduced (HFmrEF), normal (HFnEF) and, perhaps, supra-normal (HFsnEF) LVEF.[50] Analyses of >350 000 routinely collected echocardiograms suggested that the nadir of risk, whether or not the patient has a diagnosis of heart failure, lies in the range 60–65% both for men and women. Interestingly, an LVEF of >70% was associated with similar risk as an LVEF of 30–40% (**Figure 2**).[50]

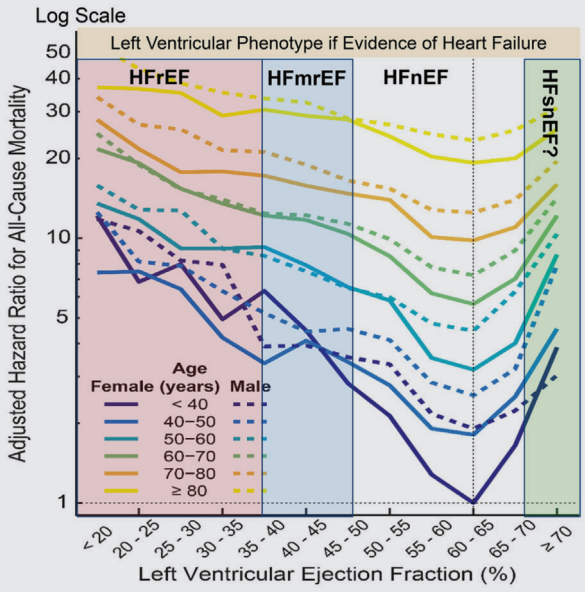


FIGURE 2. All-cause mortality according to left ventricular ejection fraction reported on >350 000 routine echocardiograms stratified by age and sex.

HFmrEF, heart failure with mildly reduced ejection fraction; HFnEF, heart failure with normal ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFsnEF, heart failure with supra-normal ejection fraction. Reproduced with permission from ref.[50]

Smjernice ESC-a iz 2016. godine uvele su koncept HFmrEF zbog dvaju glavnih razloga. Prvo, zbog nepreciznosti, ehokardiografska se mjerenja ne mogu pouzdano razlikovati između dvaju mjerenja LVEF-a unutar 10 % od svakog. Stvaranjem međuzone između HFrEF-a i HFnEF-a znači da će pogreške pri klasifikaciji biti manje vjerojatne. Ova inovacija znači da studije za HFpEF ne mogu potvrditi dobrobit za sve bolesnika s LVEF-om >40 % temeljeno samo na učinku u oboljelih s vrijednostima LVEF 40 – 49 %. Drugo, uvođenje HFmrEF-a dovodi u pitanje dogovor da je LVEF <40 % bila dobro postavljena granica za HFrEF. Neke naknadne analize ESC-ovih smjerni-

The ESC Guidelines of 2016 introduced the concept of HFmrEF, for two main reasons. Firstly, because of imprecision, an echocardiographic measurement could not reliably distinguish between two measurements of LVEF within 10% of each other. Creating a buffer-zone between HFrEF and HFnEF meant that misclassification was less likely. This innovation meant that a trial of HFpEF could not claim benefit for all patients with an LVEF >40% based solely on an effect in those with an LVEF 40–49%. Secondly, the introduction of HFmrEF challenged the convention that an LVEF <40% was the correct threshold for HFrEF. Some analyses subsequent to the ESC

ca iz 2016. pokazuju da bi bolesnici s LVEF-om <50 % mogli imati sličan odgovor na liječenje kao oni s LVEF-om <40 %.[51] Međutim, ovakva bi interpretacija mogla odražavati konfirmacijski bias zagovaratelja HFmrEF-a (**tablica 1**). Dokazi nisu dosljedni kada se gledaju u potpunosti, posebice ako se mortalitet smatra ključnim ishodom. U budućnosti će mnoga istraživanja vjerojatno uključiti i HFrEF i HFmrEF, druge će uključiti HFmrEF, HFnEF i HFsnEF, ali NT-proBNP trebao bi se rabiti rutinski za stratifikaciju rizika i potencijalno isključenje niskorizičnih bolesnika, koji bi imali malo koristi od još jedne „tablete". Pretpostavljajući da nastavljamo s uporabom LVEF-a za klasifikaciju bolesnika, što se čini vjerojatnim jer ne možemo mijenjati prošlost, tada je glavno pitanje postavljanje granica. Za HFrEF one su bile u rasponu od <25 % u *COPERNICUS*, <30 % u *MADIT-II* i *RAFT* te <35 – 40 % za većinu ostalih studija.[51] Za HFpEF vrijednost LVEF-a uglavnom je postavljena na

2016 Guideline suggest that patients with an LVEF <50% may respond to treatment similarly to those with an LVEF <40%.[51] However, this interpretation could reflect confirmation-bias amongst enthusiastic proponents of HFmrEF (**Table 1**). The evidence is not so consistent when looked at in its entirety, especially if mortality is considered a key outcome. In the future, many trials will probably include both HFrEF and HFmrEF, others will include HFmrEF, HFnEF, and HFsnEF, but NT-proBNP should be used routinely to stratify risk and potentially exclude low-risk patients who have little to gain from yet another 'pill'. Assuming we continue to use LVEF to classify patients, which seems likely since we cannot undo the past, then the major issue is where to set thresholds. For HFrEF, these have ranged from <25% in COPERNICUS, <30% in MADIT-II, and RAFT to <35–40% for the bulk of other trials.[51] For HFpEF, LVEF has generally been set at >40% or >45%

TABLE 1. Evidence supporting or refuting the benefits of treatments for heart failure with a left ventricular ejection fraction in the "mid-range" (HFmrEF: 40–49%).

	LVEF	Symptoms	Hospitalization for heart failure[a]	CV death or HFH[a]	CV mortality	All-cause mortality
Diuretics						
Perindopril		**Improved**		**0.38 (0.19–0.75)**[b]		
Candesartan		**Improved**	**0.72 (0.55–0.95)∏**	**0.76 (0.61–0.96)**	0.81 (0.60–1.11)	0.79 (0.60–1.04)
Irbesartan				0.98 (0.85–1.12)Δ		
ARNI (Sac/Val) vs. Val[c]		**Improved**	0.77 (0.58–1.02)	0.81 (0.64–1.03)	0.94 (0.69–1.28)	NYR
MRA (overall)[c]			0.76 (0.46–1.27)	0.72 (0.50–1.05)	0.69 (0.43–1.12)	0.73 (0.49–1.10)
MRA (Americas)[c]			0.60 (0.32–1.10)	**0.55 (0.33–0.91)**	**0.46 (0.23–0.94)**	**0.58 (0.34–0.99)**
ß-Blocker (SR)	**Improved**		0.95 (0.68–1.32)	0.83 (0.60–1.13)	**0.48 (0.24–0.97)**	0.59 (0.34–1.03)
ß-Blocker (AF)	**Improved**		1.15 (0.57–2.32)	1.06 (0.58–1.94)	0.86 (0.36–2.03)	1.30 (0.63–2.67)
Ivabradine						
Digoxin			0.80 (0.63–1.03)	0.96 (0.79–1.17)	1.24 (0.94–1.64)	1.08 (0.85–1.37)
Rivaroxaban *vs.* aspirin			0.65 (0.40–1.05)			0.75 (0.53–1.06)
Rivaroxaban+Aspirin *vs.* aspirin			0.87 (0.56–1.35)			**0.63 (0.44–0.90)**
CRT						
ICD						
BNP-guided therapy				**Reduction from 67% to 44% patients with an event**		

Statistically significant results are shown in bold on a blue background. Blank cells indicate no relevant information reported. Other data shown are not significant, although may not be heterogeneous with the effect in patients with a reduced left ventricular ejection fraction (HFrEF). Data for sacubitril/valsartan taken from reference for LVEF >42.5% to 52.5%.[98]

AF, atrial fibrillation; ARNI, angiotensin receptor-neprilysin inhibitors; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MRA, Mineralocorticoid receptor antagonist; SR, sinus rhythm.

[a]Recurrent event analyses used when available.

[b]The PEP-CHF trial specified inclusion of patients with LVEF 40–49% as was LVEF >49% but did not report effects in this subgroup. However, it did report effects in patients with a prior myocardial infarction who were more likely to have HFmrEF.

[c]Stronger effect in women.

>40 % ili >45 % bez gornjeg limita. Analiza novijih istraživanja dovela je neke do prijedloga da bi se za bolesnike s povišenom vrijednosti NT-proBNP-a gornji limit LVEF-a za HFmrEF trebao povisiti na 55 % ili čak na 60 %, ali se to čini preuranjeno dok se konzistentnost dokazuje uz razne intervencije i ishode i preciznost mjerenja LVEF-a se poboljšava.

U važnoj opservacijskoj studiji bolesnika s HFpEF-om i plućnom hipertenzijom uočena je progresija disfunkcije desne klijetke (RV) više nego LV uz povećani rizik od fibrilacije atrija (AF) i smrti.[52] Iako je disfunkcija RV-a jak prognostički pokazatelj, objavljeno je vrlo malo studija u kojima je istraživana disfunkcija RV-a (*SERENADE: https://clinicaltrials.gov/ct2/show/NCT03153111*).

Fibrilacija atrija

Oko trećina izvanbolničkih bolesnika, moguće više onih s HFpEF-om,[53] i više od polovice hospitaliziranih zbog HF-a imat će AF, što je povezano s nepovoljnom prognozom čak kada se napravi korekcija za životnu dob i ostale čimbenike rizika.[54] Nastavlja se polemika je li medicinsko liječenje usmjereno na kontrolu frekvencije ili postizanje sinusnog ritma bolja strategija za AF i HF. U praksi strategija liječenja treba biti prilagođena bolesniku. Ako je AF uzrok simptoma i pogoršava funkciju srca, tada je uspostava sinus-ritma odgovarajući izbor, ali, ako je AF pokazatelj progresije postojeće disfunkcije srca, tada možda nije.[55] Kod novonastale ili paroksizmalne AF povezane s jasnim pogoršanjem simptoma, uspostava sinusnog ritma opravdana je u svrhu poboljšanja simptoma. Kod dugotrajne AF i HF sa znatno dilatiranim atrijima postojano održanje sinusnog ritma i kontrakcije atrija manje je vjerojatno. Optimalno farmakološko liječenje uključuje antikoagulantnu terapiju, izbjegavanje toksičnih antiaritmijskih lijekova i kontrolu frekvencije klijetki bez strogih limita. Beta-blokatori su lijekovi izbora za kontrolu frekvencije. Frekvencija danju u mirovanju trebala bi biti od 70 do 90/min,[49] što može zahtijevati samo malu dozu; digoksin bi se, ako se uopće rabi, trebao primjenjivati poštedno. Nažalost, randomizirane studije usporedbe strategije kontrole frekvencije s obzirom na kontrolu ritma AF-a nisu uspjela optimizirati strategiju kontrole frekvencije na gore opisan način.

Metaanaliza randomiziranih studija usporedbe strategije kontrole frekvencije s obzirom na kontrolu ritma AF-a uključila je četiri studije (n = 2486) i, uspoređujući farmakološku kontrolu ritma i frekvencije, nije utvrdila razliku u mortalitetu ili tromboembolijskim događajima, ali je povećan broj hospitalizacija, često zbog ponavljajuće AF u grupi s kontrolom ritma.[56] Šest istraživanja (n = 1112) uspoređivalo je AF ablaciju s kontrolom frekvencije i utvrdilo smanjenje mortaliteta (0,51; 95% CI 0,36 – 0,74), broja hospitalizacija (0,44; 95% CI 0,26 – 0,76), moždanih udara (0,59: 95% CI 0,23 – 1,51) i poboljšanje kvalitete života.[56] Međutim, nijedno od tih istraživanja pojedinačno nema jake rezultate, bolesnici su bili strogo birani i strategija kontrole frekvencije nije bila optimalna. Stoga se spomenuta metaanaliza treba shvatiti na razini stvaranja hipoteze. Potrebna su daljnja istraživanja uz veće uključivanje liječnika koji se bave HF-om.

Implantabilni električni uređaji

Polemika se o ulozi uređaja s isporukom energije kod HF-a nastavlja. Dugotrajno praćenje resinkronizacijeke terapije

with no upper limit. Analyses of recent trials have led some to suggest that, for patients with an elevated NT-proBNP, the upper limit of LVEF for HFmrEF should be increased to 55% or even 60% but this seems premature until consistency is demonstrated across multiple interventions and end-points and measurement precision for LVEF improves.

In a substantial observational study of patients with HFpEF and pulmonary hypertension, progression of right rather than left ventricular dysfunction was observed and was associated with an increased risk of atrial fibrillation (AF) and death.[52] Although right ventricular (RV) dysfunction is a powerful prognostic marker, remarkably few trials focusing on RV dysfunction have been done (SERENADE: *https://clinicaltrials.gov/ct2/show/NCT03153111*).

Atrial fibrillation

About a third of outpatients, perhaps more for those with HFpEF,[53] and more than half of those admitted with heart failure will be in AF, which is associated with an adverse prognosis even after correcting for age and other risk factors.[54] Controversy continues over whether medical management focused on rate control or restoration of sinus rhythm is the better strategy for AF and heart failure. In practice, the strategy needs to be tailored to the patient. When AF is the driver of symptoms and worsening cardiac function, restoration of sinus rhythm might be appropriate but when AF reflects the progression of underlying cardiac dysfunction, it may not.[55] For new-onset or paroxysmal AF associated with a clear deterioration in symptoms, restoration of sinus rhythm may be warranted to improve symptoms. For long-standing AF and heart failure with markedly dilated atria, sustained restoration of sinus rhythm and atrial contraction is less likely. Optimal pharmacological management includes anticoagulation, avoiding toxic anti-arrhythmic agents and lenient ventricular rate control. Beta-blockers are the agent of choice for rate control, a resting day-time ventricular rate of 70–90 b.p.m. is preferred,[49] which may require only modest doses; digoxin should be used sparingly, if at all. Unfortunately, RCTs of rate vs. rhythm control for AF have failed to optimize the rate control strategy in the above fashion.

A meta-analysis of RCTs of rate vs. rhythm control included four trials (n = 2486) comparing pharmacological rhythm to rate control found no difference in mortality or thromboembolic events but an increase in hospitalizations, often due to recurrent AF, in the rhythm control group.[56] Six trials (n = 1112) comparing AF ablation with rate control reported reductions in mortality (0.51; 95% CI 0.36–0.74), hospitalizations (0.44; 95% CI 0.26–0.76), and stroke (0.59: 95% CI 0.23–1.51) and an improved quality of life.[56] However, none of the trials individually had a robust result, patients were highly selected and the rate control strategy was not optimal. As such, this meta-analysis should be considered hypothesis generating. Further trials are required with greater involvement of heart failure physicians.

Implanted electrical devices

The controversy over the role of high-energy devices for heart failure continues. Long-term follow-up of cardiac resynchronization therapy (CRT) in a French Registry showed a low rate of sudden death amongst patients who received

srca (CRT) u Francuskom registru pokazalo je nisku učestalost iznenadne smrti u bolesnika koji su imali RCT-Pacing (bez defibrilatora).[57-59] Sustavan pregled opservacijskih i randomiziranih istraživanja pokazuje da se razlika u učestalosti iznenadne smrti između CRT-Pacinga i CRT-D-a smanjuje.[58] Randomizirane studije usporedbe CRT-Pacinga i CRT-D-a su u tijeku[59] (**slika A** – *Take home figure*). U tijeku je i istraživanje (*CMR_GUIDE; https://clinicaltrials.gov/ct2/show/NCT01918215*) koje bi trebalo utvrditi da li ožiljak miokarda utvrđen na magnetnoj rezonanciji identificira bolesnike koji bi imali veću korist od implantabilnog kardioverterskog defibrilatora (ICD)[60]. Retrospektivna analiza studije *SCD-HeFT* pokazala je da bolesnici s T2DM-om nisu imali korist od ICD-a.[61] Metaanaliza individualnih podataka bolesnika potvrdila je smanjenje iznenadne smrti uz MRA.[62] Sustavnim su pretraživanjem identificirane 22 studije s analizom ICD uređaja nakon smrti; analiza je pokazala da 24 % smrti nije bilo aritmogeno.[63] Vrijedno istraživanje sa stimulacijom na više mjesta, do sada, nije pokazalo poboljšanja u kliničkom ili ehokardiografskom odgovoru u usporedbi s CRT-om.[64]

Mitralna regurgitacija

Istraživanje *COAPT* pokazalo je da bi perkutano postavljen MitraClip mogao smanjiti funkcionalnu (sekundarnu) regurgitaciju s posljedičnim znatnim poboljšanjem morbiditeta i mortaliteta, što je davalo umjerenu korist u odnosu između učinka i troška u kontekstu američkog zdravstvenog sustava (361 USD po dobivenoj godini života i 55 600 USD po dobivenoj kvalitetnoj godina života).[65-68] Dvije godine praćenja *MITRA. fr* nisu pokazale dobrobit.[69] Moguće objašnjenje očite razlike moglo bi biti s obzirom na težinu disfunkcije LV-a i težinu mitralne regurgitacije. Ako je regurgitacija disproporcionalna težini disfunkcije LV-a, to može dovesti do progresije i korekcija može poboljšati ishod.[70,71] Kad je regurgitacija razmjerna težini disfunkcije LV-a, popravak mitralne regurgitacije mogao bi biti manje koristan jer disfunkcija miokarda dovodi do progresije bolesti. Sam je koncept jednostavan i prihvatljiv, ali primjena u praksi može biti kompliciranа. Mitralna regurgitacija rastereću lijevu klijetku i može maskirati disfunkciju. Isto tako je vjerojatno da postoji spektar primarne i sekundarne mitralne regurgitacije te u nekih bolesnika i mješovita slika. Više iskustva i budućih podataka iz randomiziranih studija moglo bi poboljšati izbor bolesnika (*RESHAPE-HF2: https://clinicaltrials.gov/ct2/show/NCT02444338*). Kakogod, optimizacija terapije preporučene u smjernicama, uključujući doze diuretika, mogla bi uzrok mitralne regurgitacije sekundarno zbog dilatacije LV-a i mitralnog prstena poboljšati i riješiti. Razvijaju se i druge tehnologije za sekundarnu mitralnu[72] i trikuspidalnu regurgitaciju.[73,74]

Koronarna bolest srca

U studiji *COMPASS* (n = 27 395) 5902 bolesnika s CAD-om u sinusnom ritmu i s dijagnozom HF-a (uglavnom HFpEF) bila su randomizirana na acetilsalicilatnu kiselinu (ASK) 100 mg na dan, rivaroksaban 2 x 5 mg ili ASK i rivaroksaban 2 x 2,5 mg.[75,76] Istraživanje je prekinuto ranije zbog boljega primarnog ishoda (kombinirani ishod smrti od CV-a, moždanog udara ili infarkta miokarda) uz kombinaciju lijekova u usporedbi sa samom ASK. Daljnje su analize pokazale smanjenje sveukupne smrtnosti u bolesnika s HF-om, posebice HFpEF-om,

CRT-Pacing (without a defibrillator).[57–59] A systematic review of observational studies and RCTs reported that differences in the rate of sudden death with CRT-Pacing and CRT-D were narrowing.[58] RCTs comparing CRT-Pacing and CRT-D are underway[59] (**Figure A** – *Take home figure*). Whether myocardial scar found on cardiac magnetic resonance imaging identifies patients with more to gain from an implantable cardioverter defibrillator (ICD) is also under investigation[60] (CMR_GUIDE; *https://clinicaltrials.gov/ct2/show/NCT01918215*). Retrospective analysis of SCD-HeFT found that patients with T2DM did not benefit from an ICD.[61] An individual patient-data meta-analysis confirmed a reduction in sudden death with MRA.[62] A systematic review identified 22 studies with post-mortem interrogation of ICDs; the analysis suggested that 24% of sudden deaths were not arrhythmic.[63] A substantial multipoint pacing trial failed, so far, to show improvements in the clinical or echocardiographic response to CRT.[64]

Mitral regurgitation

COAPT suggested that a percutaneously delivered mitral clip could reduce functional (secondary) regurgitation with a subsequent substantial improvement in morbidity and mortality that was moderately cost-effective in a US healthcare context (US$40 361 per life-year gained and $55 600 per quality-adjusted life year).[65–68] Two-year follow-up of MITRA.fr suggested no benefit.[69] A possible explanation for the apparent discrepancy could be the ratio of the severity of LV dysfunction to the severity of mitral regurgitation. When regurgitation is disproportionate to the severity of LV dysfunction it may drive disease progression and correction may improve outcome.[70,71] When regurgitation is proportionate to the severity of LV dysfunction, fixing the mitral regurgitation may be less useful because myocardial dysfunction drives disease progression. The concept is simple and plausible but application in practice may be difficult. Mitral regurgitation offloads the LV and may mask dysfunction. It is also likely that there is a spectrum of primary and secondary mitral regurgitation, with some patients having a mixed picture. More experience and further data from RCTs may improve patient selection (RESHAPE-HF2: *https://clinicaltrials.gov/ct2/show/NCT02444338*). However, optimizing guideline-recommended therapy, including diuretic dose, may cause mitral regurgitation secondary to dilation of the LV and mitral ring to improve or resolve. Other technologies for secondary mitral[72] and tricuspid regurgitation[73,74] are being developed.

Coronary artery disease

In COMPASS (n = 27 395), 5902 with CAD, in sinus rhythm and with a diagnosis of heart failure (predominantly HFpEF) were randomly assigned them to aspirin 100 mg/day, rivaroxaban 5 mg bd or aspirin and rivaroxaban 2.5 mg bd.[75,76] The study was stopped early for benefit on the primary endpoint (a composite of CV death, stroke, or myocardial infarction) with the combination compared with aspirin alone. Further analysis suggested a reduction in all-cause mortality for patients with heart failure, especially HFpEF, assigned to combination therapy (HR: 0.63; 0.44–0.90) or rivaroxaban alone (HR: 0.75; 0.53–1.06) with an estimated 4% absolute difference at 2 years; rather similar to the magnitude of effect in HFrEF for sacubitril-valsartan[77] or dapagliflozin[78]

koji su bili na kombinaciji lijekova (HR: 0,63; 0,44 – 0,90) ili samom rivaroksabanu (HR: 0,75; 0,53 – 1,06) s procjenom 4 % apsolutne razlike za 2 godine; prilično slično jačini učinka sakubitril-valsartana[77] kod HFrEF-a ili dapagliflozina[78] (**slika 3**). Ovo upućuje na to da su koronarni događaji važni uzroci smrti kod HFpEF-a (**slika A** – *Take home figure*), iako se ne smije umanjiti učinak rivaroksabana na endotelnu funkciju, upalu i fibrozu. Analiza isto tako pokazuje da bolesnici koji nemaju HF imaju malu korist od dodatnog liječenja rivaroksabanom.

(**Figure 3**). This suggests that coronary events might be an important driver of death in HFpEF (**Figure A** –*Take home figure*), although effects of rivaroxaban on endothelial function, inflammation, and fibrosis should not be discounted. The analysis also suggests that those who do not have heart failure have little to gain from additional treatment with rivaroxaban.

FIGURE 3. Please see the original article (Eur Heart J. 2020 Mar 21;41(12):1232-1248.).

Međutim, u bolesnika s HFrEF-om, CAD-om, u sinusnom ritmu te nedavno otpuštenih iz bolnice zbog pogoršanja HF-a, dodatak rivaroksabana 2 x 2,5 mg uz osnovnu antitrombotsku terapiju nije poboljšalo ukupnu prognozu, usprkos tomu što je kombinirani vaskularni ishod (moždani udar, infarkt miokarda i iznenadna smrt) bio smanjen, uglavnom zbog smanjenja moždanih udara.[79,80] Ovo pokazuje da u bolesnika sa stabilnom CAD i uznapredovalom HF broj hospitalizacija i smrtni ishod zbog pogoršanja HF-a nisu pod velikim utjecajem antitrombotske terapije (**slika A** – Take home figure).

Inhibitori angiotenzinskih receptora i neprilizina

Zatajivanje srca sa sniženom istisnom frakcijom

Kako se povećava iskustvo s uporabom inhibitora angiotenzinskih receptora i neprilizina (ARNI) u kliničkim istraživanjima i u svakodnevnoj praksi, tako imamo jak argument da razmislimo o njima kao o lijekovima prve linije prije nego inhibitorima enzima konvertaze angiotenzina (ACE) i blokatorima anigiotenzinskih receptora (ARB) za liječenje HFrEF-a. U istraživanje *PIONEER-HF*[81] bio je uključen 881 bolesnik s LVEF-om ≤40 % koji su bili hospitalizirani zbog pogoršanja funkcije srca, a bili su randomizirani bez uvodnog razdoblja, neposredno prije otpusta na sakubitril-valsartan ili enalapril. Tijekom praćenja od 8 tjedana promatrao se učinak na vrijednost NT-proBNP-a, a jedna je trećina imala novonastalo HF. Uz sakubitril-valsartan postignuto je veće smanjenje vrijednosti NT-proBNP-a. Primijećeno je i smanjenje markera oštećenja ili stresa miokarda, visoko osjetljivog toponina-T i topljivog ST2. Ovakvi su se učinci pojavili brzo nakon randomizacije (unutar 1 – 4 tjedna). Osim toga, bolesnici koji su bili na sakubitril-valsartanu imali su manju vjerojatnost pojave nepovoljnih događaja unutar prvih 8 tjedana. U studiji *TRANSITION*[82] bilo su 1002 bolesnika randomizirana na započinjanje terapije sakubitril-valsartanom prije ili nakon otpusta iz bolnice, utvrdivši da ranije uvođenje terapije nije imalo neželjene učinke.

Studija *EVALUATE*[83] uspoređivala je učinak sakubitril-valsartana i enalaprila na krutost aorte kod HFrEF-a, a većina

However, for patients with HFrEF, CAD in sinus rhythm with a recent hospital discharge for worsening heart failure, addition of rivaroxaban 2.5 mg bd to background anti-platelet therapy did not improve overall prognosis, although a composite of vascular outcomes (stroke, myocardial infarction, and sudden death) was reduced, driven mainly by a reduction in stroke.[79,80] This suggests that for patients with stable CAD and more advanced heart failure, hospitalizations, and deaths due to worsening heart failure are not greatly influenced by anti-thrombotic therapy (**Figure A** –*Take home figure*).

Angiotensin receptor-neprilysin inhibitors

Heart failure with reduced ejection fraction

As experience in the implementation of angiotensin receptor-neprilysin inhibitors (ARNIs) grows, both in clinical trials and in clinical practice, there is a strong argument to consider them as first-line agents, rather than angiotensin converting-enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), for the treatment of HFrEF. In PIONEER-HF,[81] 881 patients with an LVEF ≤40% who were hospitalized for worsening heart failure were randomly assigned, without a run-in period, to sacubitril/valsartan or enalapril prior to discharge and followed for 8 weeks to determine the effect on plasma concentrations of NT-proBNP; about one-third had new-onset heart failure. Sacubitril-valsartan exerted a greater reduction in NT-proBNP. Reductions in markers of myocardial injury or stress, high-sensitivity cardiac troponin-T and soluble ST2, were also observed. These effects appeared early after randomization (within 1–4 weeks). Moreover, patients assigned to sacubitril/valsartan were less likely to experience adverse outcomes within the first 8 weeks. TRANSITION[82] randomly assigned 1002 patients to pre- or post-discharge initiation of sacubitril/valsartan, showing no adverse consequences to earlier administration.

EVALUATE[83] compared the effects of sacubitril/valsartan and enalapril on aortic stiffness in HFrEF most of whom were already chronically treated with an ACEi or ARB. After 24 weeks treatment, no differences in aortic stiffness were

je ispitanika otprije bila na kroničnoj terapiji uz lijekove iz skupine ACE inhibitora ili ARB. Nakon 24 tjedna liječenja nije uočena razlika u krutosti aorte, ali je primijećeno malo veće smanjenje enddijastoličkog i sistoličkog volumena LV-a u skupini na sakubitril-valsartanu u odnosu prema enalaprilu, iako su promjene u LVEF-u bile slične. Vrijednost brzine E-vala nad mitralnim zalistkom i volumen lijevog atrija smanjili su se, što je u skladu sa smanjenjem tlaka u lijevom atriju. *PROVE-HF*[84], opservacijska studija, imala je slične rezultate i prikazala je da se najveći pad NT-proBNP-a dogodio u prvih 14 dana sukladno nastupu brzoga kliničkog poboljšanja zapaženog uz sakubitril-valsartan u studijama i kliničkoj praksi. *PRIME*[85] je bila randomizirana studija (n = 118) koja je uspoređivala učinak sakubitril-valsartana ili valsartana na funkcionalnu mitralnu regurgitaciju u bolesnika s LVEF-om između 25 i 49% koji su već uzimali lijekove iz skupine ACE ili ARB. U onih koji su bili na sakubitril-valsartanu nastupilo je veće smanjenje mitralne regurgitacije i enddijastoličkog LV-a i volumena lijevog atrija, ali se LVEF podjednako malo povećala u obje skupine (oko 2,5 %).

Dodatna istraživanja iz studije *PARADIGM-HF* pokazala su da, u usporedbi s enalaprilom, sakubitril-valsartan može poboljšati parametre metabolizma kolagena, posebice, smanjenjem sinteze tipa 1 kolagena, koji znatno pridonosi krutosti miokarda.[86] U studiji *I-PRESERVE* irbesartan nije imao utjecaj na biomarkere kolagena u usporedbi s placebom.[87]

Zatajivanje srca s očuvanom istisnom frakcijom

Studija *PARAGON-HF* istraživala je učinak sakubitril-valsartana u usporedbi s primjenom valsartana na morbiditet i mortalitet u bolesnika s HFpEF-om (definirano kao LVEF >45 %).[88] To je bila prva randomizirana studija nakon *PEP-CHF*[89] koja je zahtijevala da bolesnici budu liječeni diureticima, lijekovima prve linije za poboljšanje simptoma i znakova kongestije te da imaju ehokardiografski dokaz disfunkcije srca. Isto tako, to je bila prva velika studija HFpEF-a koja je zahtijevala da svi bolesnici imaju povišenu razinu natriuretskog peptida, najsnažnijega široko dostupnog prognostičkog markera HFpEF-a. Sakubitril-valsartan uspoređivan je s valsartanom, a ne s placebom jer je mnogo bolesnika pogodnih za uključenje u studiju *PARAGON-HF* imalo indikaciju za liječenje primjenom lijekova iz skupova ACE i ARB, s obzirom na hipertenziju i CAD. Jedino istraživanje koje je uspoređivalo valsartan s placebom imalo je mali broj uključenih ispitanika i neutralan ishod.[90] Ranije randomizirane studije drugih ARB-ova, uključujući kandesartan (*CHARM-Preserved*) i irbesartan (*I-PRESERVE*), nisu uspjele dokazati značajnu dobrobit kod HFpEF-a.[88] Bolesnici su trebali prije randomizacije dobro podnositi sekvencijalno i valsartan i sakubitril/valsartan u polovici predviđene ciljne doze. Tako je simulirana klinička praksa (liječnici obično ne propisuju lijekove bolesnicima koji ih nisu voljni ili ih ne mogu uzimati) i smanjilo se rizik od neutralnog ishoda studije zbog slabe adherencije. Od 10 539 ispitanih bolesnika randomizirana su 4822 ispitanika.

Studija *PARAGON-HF* upozorila je na neutralne rezultate u vezi s primarnim zajedničkim ishodom (CV smrtnost ili ukupan broj ponavljajućih hospitalizacija zbog HF-a[91]; **slika 4**). Neki su tvrdili da je P-vrijednost vrlo blizu 0,05 i da je to „skoro" pozitivno. To je kriva interpretacija. Studija je pokazala da je veličina potencijalne koristi sakubitril-valsartana kod HFpEF-a skromna, bez obzira na P-vrijednost i da bi liječenje malo vjerojatno uopće bilo isplativo. Prema tome, moramo

observed but slightly greater reductions in LV end-diastolic and systolic volumes were observed with sacubitril/valsartan compared with enalapril, although changes in LVEF were similar. Mitral E-velocity and left atrial volume declined, consistent with a fall in left atrial pressure. PROVE-HF,[84] an observational study, had similar findings and showed that most of the decline in NT-proBNP occurred within 14 days consistent with the rapid onset of clinical benefit observed with sacubitril/valsartan in trials and clinical practice. PRIME[85] was an RCT (n = 118) comparing the effects of sacubitril/valsartan or valsartan on functional mitral regurgitation in patients with an LVEF between 25% and 49% who were already receiving an ACEi or ARB. Those assigned to sacubitril/valsartan had greater reductions in mitral regurgitation and LV end-diastolic and left atrial volumes but LVEF increased by a similar small amount in each group (about 2.5%).

Further reports from PARADIGM-HF suggest that, compared with enalapril, sacubitril/valsartan may improve markers of collagen metabolism, in particular, decreasing synthesis of type-I collagen, which makes an important contribution to myocardial stiffness.[86] In I-PRESERVE, irbesartan (an ARB) did not affect collagen biomarkers compared with placebo.[87]

Heart failure with preserved ejection fraction

PARAGON-HF investigated the effect of sacubitril/valsartan compared to valsartan alone on morbidity and mortality in patients with HFpEF (defined as an LVEF >45%).[88] It was the first RCT since PEP-CHF[89] to require patients to be treated with diuretics, the first-line treatment for the relief of symptoms and signs of congestion, and to have echocardiographic evidence of cardiac dysfunction. It was also the first large trial of HFpEF to require all patients to have raised plasma concentrations of natriuretic peptides, the most powerful, widely available prognostic marker in HFpEF. Sacubitril/valsartan was compared with valsartan rather than placebo because many patients eligible for PARAGON-HF had indications for ACE inhibitors and ARBs such as hypertension and CAD. The only trial comparing valsartan to placebo in HFpEF was of modest size and neutral.[90] Previous RCTs of other ARBs, including candesartan (CHARM-Preserved) and irbesartan (I-PRESERVE) failed to show substantial benefit for HFpEF.[88] Patients had to tolerate, sequentially, both valsartan and sacubitril/valsartan at half the intended target dose before randomization. This simulates clinical practice (doctors do not usually prescribe medicines to patients unwilling or unable to take them) and reduces the risk of a neutral trial-outcome due to low adherence. Of 10 539 patients screened, 4822 were randomized.

PARAGON-HF was neutral for its primary endpoint (CV death or the total number of recurrent hospitalizations for heart failure[91]; **Figure 4**). Some have argued that the P-value was very close to 0.05 and that it was 'almost' positive. This misses the point. The trial shows that the size of the potential benefit of sacubitril/valsartan for HFpEF is modest, regardless of the P-value and that the treatment is, overall, unlikely to be cost-effective. Accordingly, we should look for more effective treatments or, more controversially, subgroups that obtain greater benefit. After a median follow-up of 35 months, 23% of patients experienced a primary event but the annual incidence of CV and all-cause mortality were, respectively,

FIGURE 4. Please see the original article (Eur Heart J. 2020 Mar 21;41(12):1232-1248.).

tražiti još učinkovitije metode liječenja i još kontroverznije – podgrupe koje će ostvariti bolju korist. Nakon medijana praćenja od 35 mjeseci, 23 % bolesnika doživjelo je primarni ishod, ali CV mortalitet i ukupni mortalitet iznosili su samo 3 % i 5 %, što je slično podatcima iz prethodnih studija za HFpEF i starije bolesnike s rezistentnom hipertenzijom koji su bili u skupini na placebu u istraživanju *HYVET*.[92] Iako je <3 % bolesnika bilo prijavljeno da imaju HF, u spomenutom istraživanju kombinacija indapamida i perindoprila smanjila je sveukupni mortalitet i incidenciju HF-a za >50 %. Mnogi od tih bolesnika vjerojatno su imali neprepoznatu HFpEF prije randomizacije. Veća učestalost hospitalizacije zbog HF-a u odnosu prema hipertenziji u studijama s HFpEF-om mogla bi upućivati na konstatacijski bias, jer kliničari koji imaju više interesa ili su eksperti u liječenju HF-a vjerojatno će više dijagnosticirati i prijavljivati događaje u vezi s HF-om. U cjelini, spomenute studije upućuju na to da bi učestalost mortaliteta i vjerojatno kardiovaskularnih i sveukupnih hospitalizacija mogla biti slična s dijagnozom HFpEF-a ili bez nje ako bolesnici imaju slično opterećenje komorbiditetima. Međutim, isto tako je vjerojatno da mnogi bolesnici s hipertenzijom, CAD-om i T2DM-om imaju nedijagnosticiran HF.

Analize podgrupa pokazale su da je učinak sakubitril-valsartana na primarni ishod bio veći za bolesnike s LVEF-om ispod medijana (57 %), ali to je bilo postignuto gotovo u potpunosti učinkom broja hospitalizacija zbog HF-a prije nego učinkom na smrtnost od CV-a.[93] Učinak sakubitril-valsartana na primarni ishod isto je tako bio veći u žena i to je vrijedilo za sve promatrane razine LVEF-a, ali je to opet bilo ostvareno razlikom u broju hospitalizacija zbog HF-a, a ne zbog mortaliteta od CV-a.[94] Smanjenje vrijednosti NT-proBNP-a bilo je slično za oba spola. Čini se da sakubitril-valsartan ima povoljan učinak na kvalitetu života u muškaraca, ali ne u žena. Bolesnici s nedavnom hospitalizacijom zbog HF-a mogli bi imati veću dobrobit.[95] Ovakve se opservacije trebaju uspoređivati sa studijom koja je bila neutralna glede primarnih ishoda. Nisu dokazani učinak na mortalitet i korist od liječenja s obzirom na kvalitetu života, a ni na broj hospitalizacija zbog HF-a s obzirom na spol. U istraživanju *PARADIGM-HF* nije utvrđena razlika u učinku liječenja s obzirom na spol. U novoj prilično velikoj randomiziranoj studiji za HFpEF, *PARALLAX-HF*, ispitivanje učinka sakubitril-valsartana na kvalitetu života i kapacitet vježbanja dat će više podataka tijekom 2020. godine (*https://clinicaltrials.gov/ct2/show/NCT03066804*).

Imaju li žene i muškarci različit odgovor na terapiju?

Analiza 12 058 bolesnika s HFrEF-om u dvama velikim istraživanjima pokazala je da žene imaju više težih simptoma, podjednaku LVEF, ali mnogo bolju prognozu od muškaraca, čak i nakon korekcije za ključne prognostičke varijable, uključujući

only about 3% and 5%, which is similar to those for previous trials of HFpEF and for elderly patients with resistant hypertension assigned to placebo in HYVET.[92] Although <3% of patients were reported to have heart failure in HYVET, a combination of indapamide and perindopril reduced all-cause mortality and cut the incidence of heart failure by >50%. Many of these patients probably had undiagnosed HFpEF prior to randomization. Higher rates of hospitalization for heart failure in trials of HFpEF compared to hypertension may well reflect ascertainment bias, as clinicians who are interested or expert in the management of heart failure are more likely to diagnose or report heart failure events. Overall, these trials suggest that the mortality rate and possibly the rates of cardiovascular and all-cause hospitalization may be similar in patients with and without a diagnosis of HFpEF, if they have a similar burden of co-morbidities. However, it is also likely that many patients with hypertension, CAD and T2DM have undiagnosed heart failure.

Subgroup analysis suggested that the effect of sacubitril/valsartan on the primary endpoint was greater for patients with an LVEF below the median (57%), but this was driven almost entirely by an effect on hospitalization for heart failure rather than on CV death.[93] The effect of sacubitril/valsartan on the primary endpoint was also greater for women and this was true throughout the studied range of LVEF, but again this was driven by a difference in hospitalization for heart failure and not CV mortality.[94] Reductions in NT-proBNP were similar for each sex. Sacubitril/valsartan appeared to have a favourable effect on quality of life for men but not for women. Patients with a recent heart failure hospitalization may also have benefited more.[95] These observations should be interpreted in the light of a trial that was neutral for its primary endpoint. No effect was observed on mortality and the benefits of treatment on quality of life and hospitalizations for heart failure according to sex were inconsistent. In PARADIGM-HF, no difference in treatment effect according to sex was observed. A further sizeable RCT in HFpEF, PARALLAX-HF, investigating the effects of sacubitril/valsartan on quality of life and exercise capacity will provide more evidence in 2020 (*https://clinicaltrials.gov/ct2/show/NCT03066804*).

Do women and men respond differently to treatment?

An analysis of 12 058 patients with HFrEF in two large trials found that women had more severe symptoms, similar LVEF but a substantially better prognosis than men, even after adjusting for key prognostic variables including aetiology and NT-proBNP (HR: 0.68; 0.62–0.89).[96] A combined analysis of PARAGON-HF and PARADIGM-HF suggested that patients with HFrEF and HFpEF had similarly impaired quality of life but that women generally reported a worse quality of

etiologiju i vrijednost NT-proBNP-a (HR: 0,68; 0,62 – 0,89).[96] Kombinirana analiza studija *PARAGON-HF* i *PARADIGM-HF* pokazala je da bolesnici s HFrEF-om i HFpEF-om imaju podjednako narušenu kvalitetu života, ali žene općenito prijavljuju lošiju kvalitetu života nego muškarci.[97] U opservacijskoj analizi *BIOSTAT* koja je uključila bolesnike s HFrEF-o isto tako bilo je utvrđeno da žene općenito imaju bolju prognozu usprkos tomu što su im propisivane niže doze beta-blokatora i ACE inhibitora.[98] Zanimljivo, žene i muškarci imali su jednaku frekvenciju srca koja je farmakodinamski marker doze beta-blokatora. Za bolesnike s HFpEF-om u studiji *TOPCAT*, smanjenje mortaliteta, ali ne i broja hospitalizacija zbog HF-a, bilo je veće u žena, iako je ta interakcija bila statistički značajna samo za sveukupni mortalitet.[99] U studiji *PARAGON-HF* (HFpEF) žene su imale veću dobrobit od muškaraca kroz sve ispitivane razine vrijednosti LVEF-a, ali je razlika bila ostvarena više u učestalosti hospitalizacija zbog HF-s nego mortaliteta.[94] Jedna očita razlika između muškaraca i žena, gledano u prosjeku, jest tjelesna visina. Resinkronizacijska terapija srca smatra se učinkovitijom u žena nego u muškaraca, ali razlika nestaje kad se prilagodi visini.[100] Mnogi se lijekovi se izlučuju bubrezima. Procijenjena glomerularna filtracija (eGFR) indeksira se prema površini tijela (BSA), dok se to uobičajeno ne radi s dozama lijekova. Žena (ili sitniji muškarac) težine 64 kg i visine 160 cm ima BSA 1,67 m^2, prema Duboisovoj formuli, i muškarac (ili krupnija žena) težine 85 kg i visine 180 cm ima BSA 2,05 m^2. Ako oboje imaju eGFR od 60 mL/kg/m^2, tada žena (ili manji muškarac) ima neindeksiranu eGFR od 100 mL/min, a muškarac (ili veća žena) ima neindeksiran eGFR od 123 mL/min. Ako se lijek izlučuje bubregom, tada možda sitniji ljudi trebaju manju dozu za postizanje iste plazmatske koncentracije i kliničkog učinka?

Inhibitori natrij-glukoza kotransportera 2

Natrij-glukoza kotransporter protein-2 (SGLT2) nalazi se uglavnom u proksimalnom tubulu bubrega i u manjoj mjeri u drugim organima. SGLT1 je obilno prisutan u tankome crijevu i miokardu. SGLT2 inhibitori (SGTL2i) uzrokuju glukozuriju i poboljšavaju glikemiju, što je dovelo do njihova razvoja za liječenje T2DM-a i osmotske diureze, koja vodi do smanjenja volumena plazme.[101,102] SGLT1 inhibitori smanjuju crijevnu apsorpciju glukoze, što može uzrokovati proljev, ali mogu imati i povoljan učinak na utilizaciju energije u miokardu.[103] Većina SGLT2i visoko su selektivni, uključujući dafagliflozin i empagliflozin, dok je sotagliflozin manje selektivan.[103]

Studija *EMPA-REG* uključila je 7020 bolesnika s T2DM-om, oko 10 % njih imalo je HF (nije mjerena LVEF) i pokazala je da je empagliflozin smanjio rizik od hospitalizacije zbog HF-a i mortalitet.[104] Unutar nekoliko tjedana od početka uzimanja empagliflozina tjelesna težina i arterijski tlak su se smanjili, a hematokrit se povećao, u skladu s diuretskim učinkom. Randomizirane studije koje su slijedile s drugim SGLT2i u T2DM imale su slične rezultate. Metaanalize su pokazale da su SGTL2i bili hipoglikemici koji su imali najveću vjerojatnost smanjenja incidencije HF-a,[105-107] dok uz opservacijske podatke raste zabrinutost za inzulinsku terapiju.[108] Metaanaliza randomiziranih studija s empagliflozinom, kanagliflozinom i dapagliflozinom za T2DM, uključujući >30 000 bolesnika, pokazala je korist barem za one s potvrđenom CV bolesti.[109] Za ishode broja hospitalizacija zbog HF-a ili kardiovaskularne smrtnosti, godišnja je učestalost bila oko 0,6 % za 13 672

life than men.[97] In an observational analysis of patients with HFrEF, the BIOSTAT survey also found that women generally had a better prognosis than men despite being prescribed lower doses of beta-blockers and ACE inhibitors.[98] Interestingly, men and women had the same heart rate, the pharmacodynamic marker of beta-blocker dose. For patients with HFpEF in the TOPCAT trial, reductions in mortality, but not hospitalizations for heart failure, were greater for women, although the interaction was statistically significant only for all-cause mortality.[99] In the PARAGON-HF trial (HFpEF), women obtained greater benefit than men throughout the studied range of LVEF but the difference was driven by differences in the rate of hospitalization for heart failure rather than mortality.[94] One obvious difference between men and women, on average, is size. Cardiac resynchronization therapy is reputed to be more effective in women than men, but differences disappear once adjusted for height.[100] Many medicines are cleared by the kidney. Estimated glomerular filtration rate (eGFR) is indexed to body surface area (BSA) but doses of treatment are usually not. A woman (or small man) weighing 64 kg and 160 cm tall has BSA of 1.67 m^2 using the Dubois formula and a man (or large woman) weighing 85 kg and 180 cm tall has a BSA 2.05 m^2. If both have an eGFR of 60 mL/kg/m^2, then the woman (or small man) has an un-indexed eGFR of 100 mL/min and the man (or large woman) has an un-indexed eGFR of 123 mL/min. If a medicine is cleared by the kidney then perhaps smaller people require lower doses to achieve the same plasma therapeutic concentration and clinical benefit?

Sodium-glucose cotransporter-2 inhibitors

Sodium-glucose cotransporter protein-2 (SGLT2) is found mainly in the proximal renal tubule and to a lesser extent in other organs. SGLT1 is abundant in the intestine and myocardium. SGLT2 inhibitors (SGLT2i) cause glycosuria, improving glycaemia, which led to their development for the treatment of T2DM, and an osmotic diuresis, leading to a contraction of plasma volume.[101,102] SGLT1 inhibitors reduce intestinal glucose absorption, which can cause diarrhoea but might have favourable effects on myocardial energy-utilization.[103] Most SGLT2i are highly selective, including dapagliflozin and empagliflozin, but sotagliflozin is less selective.[103]

EMPA-REG enrolled 7020 patients with T2DM, about 10% of whom had heart failure (LVEF was not measured) and showed that empagliflozin reduced the risk of hospitalization for heart failure and mortality.[104] Within a few weeks of initiating empagliflozin, body weight, and blood pressure fell and haematocrit rose, consistent with a diuretic effect. Subsequent RCTs of other SGLT2i in T2DM had similar findings. Meta-analyses suggested that SGLT2i were the hypoglycaemic agents most likely to reduce incident heart failure,[105–107] whilst observational data raises concerns about insulin therapy.[108] A meta-analysis of RCTs of empagliflozin, canagliflozin, and dapagliflozin for T2DM, including >30 000 patients, showed benefit, at least for those with established CV disease.[109] For the outcome of hospitalization for heart failure or CV death, the annual rate was about 0.6% for the 13 672 patients with multiple risk factors but without established CV disease, about 3% for the 20 650 patients with established atherosclerotic disease and about 6% for 3891 patients with heart failure at baseline; the relative risk reductions

bolesnika s više čimbenika rizika, ali bez potvrđene CV bolesti, oko 3 % za 20 650 bolesnika s potvrđenom aterosklerotskom bolesti i oko 6 % za 3891 bolesnika sa slikom HF-a koja je poznata od početka; smanjenje relativnog rizika sa SGLT2i u ovim skupinama bile su redom 16 %, 24 % i 29 %, bez dokaza razlike između lijekova. Najveća od tih, studija *DECLARE*[110], uključila je 17 160 bolesnika, od kojih je 671 imao HFrEF, a 1316 imalo HFpEF ili neodređenu LVEF. U analizi podgrupa[111] dapagliflozin je smanjio broj hospitalizacija zbog HF-a i kardiovaskularnu smrtnost za HFrEF, ali ne za druge grupe bolesnike (**slika 5**).

with SGLT2i in these populations were 16%, 24%, and 29%, respectively, without evidence of heterogeneity amongst agents. The largest of these trials, DECLARE,[110] included 17 160 patients of whom 671 had HFrEF and 1316 had HFpEF or an unspecified LVEF. In a subgroup analysis,[111] dapagliflozin reduced hospitalizations for heart failure and CV mortality for HFrEF but not for other patient-groups (**Figure 5**).

FIGURE 5. Please see the original article (Eur Heart J. 2020 Mar 21;41(12):1232-1248.).

Studija *DAPA-HF*[78,112] bila je uključila 4744 bolesnika i pratila ih je kroz medijan od 18,3 mjeseci, pokazavši da se uz dodatak dapagliflozina terapiji, sukladno smjernicama za HFrEF, smanjio broj hospitalizacija zbog HF-a za 30 % i mortaliteta (uglavnom kardiovaskularnog) za 18 %, preveniranja 3 – 5 hospitalizacija i 1 – 2 smrti na 100 bolesnika liječenih godinu dana (**slika 6**). Bolesnici su imali i nešto manju vjerojatnost razvoja neželjenih događaja, posebice bubrežnih, uz dapagliflozin u usporedbi s placebom. Taj dobar učinak čini se postojan u svim podgrupama, iako su bolesnici s dokazom većega stupnja kongestije (viša NYHA klasa ili viša vrijednost NT-proBNP) možda imali manje koristi. Važno, učinci su bili slični za one s T2DM-om i bez njega i neovisno o životnoj dobi.[113] Dapagliflozin je isto tako poboljšao kvalitetu života,[114] učinak je potvrđen i u manjem randomiziranom istraživanju (*DEFINE*)[115] koje je pratilo 263 bolesnika tijekom 12 tjedana; oko 1 od 6 bolesnika osjećalo je znatnu korist ili prevencijom pogoršanja ili poboljšanjem simptoma u usporedbi s placebom.

DAPA-HF[78,112] enrolled 4744 patients and followed them for a median of 18.3 months, demonstrating that addition of dapagliflozin to guideline-recommended therapy for HFrEF-reduced hospitalizations for heart failure by 30% and mortality (mainly cardiovascular) by 18%, preventing 3–5 hospitalizations and 1–2 deaths per 100 patients treated per year (**Figure 6**). Patients were somewhat less likely to experience serious adverse events, especially renal, with dapagliflozin compared with placebo. The benefits appeared consistent across subgroups, although patients with evidence of more severe congestion (worse NYHA class or higher NT-proBNP) may have received less benefit. Importantly, benefits were similar for those with and without T2DM and regardless of age.[113] Dapagliflozin also improved quality of life,[114] an effect that was confirmed in a smaller RCT (DEFINE)[115] that followed 263 patients for 12 weeks; about one in six patients got a meaningful benefit, either prevention of worsening or an improvement in symptoms, compared with placebo.

FIGURE 6. Please see the original article (Eur Heart J. 2020 Mar 21;41(12):1232-1248.).

U studiji *DAPA-HF*, uz korekciju prema placebu, gubitak težine od početka do 8 mjeseci istraživanja bio je 0,87 kg i to je bilo povezano s malim padom vrijednosti NT-proBNP-a i sistoličkog tlaka i malog porasta hematokrita i kreatinina. Ovakvi su rezultati opet sukladni vjerovanju da SGLT2i ostvaruju barem neki od svojih učinaka potičući diurezu ili kroz osmotski efekt glukozurije ili upletanjem u natrij-glukoza izmjenu u nefronu.[116] Učinak SGTL2i pojavljuje se rano, što je u skladu s neposrednim hemodinamskim učinkom. Međutim, predložena su i alternativna ili dodatna objašnjenja učinka SGLT2i. Malo randomizirano istraživanje pokazalo je

In DAPA-HF, the placebo-corrected decline in weight between baseline and 8 months was 0.87 kg and this was associated with a small fall in NT-proBNP and systolic blood pressure and a small increase in haematocrit and serum creatinine. These findings are again consistent with the belief that SGLT2i exert at least some of their benefits by enhancing diuresis, either through an osmotic effect of glycosuria or by interfering with sodium-hydrogen exchange in the nephron.[116] The effects of SGLT2i appear early, consistent with an immediate haemodynamic effect. However, alternative or additional explanations for the effect of SGLT2i have

da empagliflozin stimulira produkciju eritropoetina uzrokujući porast hematokrita i pad feritina, markera upale i manjka željeza, ali ne i saturacije transferina, markera samog manjka željeza.[117] Međutim, primjena egzogenog eritropoetina nije smanjila morbiditet i mortalitet u studiji *RED-HF*.[118] Drugi su autori pretpostavljali da SGLT2i povećavaju proizvodnju ketona, koji bi mogli biti efikasniji energijski supstrat miokarda ili blokiraju natrij-glukoza izmjenjivač 3, što bi moglo dovesti do poboljšanja funkcije miokarda i smanjene fibroze.[119,120]

Jedna randomizirana studija empagliflozina u bolesnika s T2DM-om, ali bez HF-a[121], pokazala je mali učinak na funkciju srca i remodeliranje; randomizirana istzraživanja učinka SGLT2i na funkciju srca u bolesnika s HFrEF-om i HFpEF-om tek se očekuju. Buduće studije potvrdit će je li učinak uočen u studiji *DAPA-HF* efekt klase i jesu li učinkoviti kod HFpEF-a ili kad je prisutan teži stupanj kongestije.[122,123]

Akutno zatajivanje srca

Dvije velike randomizirane studije koje su ispitivale serelexin nisu uspjele potvrditi rezultate originalne studije *RELAX-AHF*. Randomizirana studija otvorenog tipa *RELAX-AHF-EU*[124] (n = 2688), izvijestila je o sličnoj ili manjoj učestalosti smrtnosti (≤2 %) i ponovnoj hospitalizaciji zbog HF-a (<1 %) kroz 14 dana za bolesnike u skupini na placebu ili serelaxinu, usprkos smanjenju pogoršanja HF petog dana liječenja [6,7 – 4,5% (P < 0,008)]. Studija *RELAX-AHF-2*[125] bila je dvostruko slijepa RCT studija (n = 6545), a utvrdila je da su učestalost pogoršanja HF-a u prvih 5 dana (oko 7 %) i 180-dnevna smrtnost (oko 11 %) bile slične i za placebo i za serelaxin. Neuspjeh tolikih kratkoročnih intervencija pri akutnom zatajivanju srca (AHF) može biti odraz promašenoga terapijskog koncepta, neučinkovitih intervencija ili problema s dizajnom studije. Randomizirane kontrolirane studije kod AHF-a teško su izvedive, posebice ako se provode dvostruko slijepo. Doista, studija *GALACTIC* istraživala je učinak personalizirane, rane intenzivne i trajne vazodilatacije primjenom nitrata i hidralazina te također nije uspjela dokazati dobrobit, dovodeći u pitanje koncept terapije vazodilatatorima pri rutinskom liječenju AHF-a.[126] Mnogi se bolesnici prikazuju noćnom zaduhom. Teško je imati na raspolaganju ekipu istraživača dostupnu 24/7 kad ne postoji „ulazna baza" slična koronarnoj jedinici ili kateterizacijskom laboratoriju. Samilosni istraživači mogli bi isto tako biti manje voljni uključivati u studiju nemoćne starije ljude koji imaju najveći rizik od nepovoljnih ishoda. Osim toga, nedostatak zraka obično reagira na terapiju kisikom i diureticima tijekom nekoliko sati,[127] posebice u bolesnika sa sistoličkim tlakom ≥125 mmHg, kao što je bilo traženo u istraživanjima sa serelaxinom. S druge strane, bolesnici s opsežnim perifernim edemima,[26] zatajenjem bubrega i niskim tlakom često ne znače akutno hitno stanje, imaju lošu prognozu i nedostatne efikasnije intervencije lijekovima ili uređajima.[127-129]

Terapija matičnim stanicama

Intramiokardijalne injekcije matičih stanica nisu uspjele pomoći pri odvajanju od uređaja za potporu funkcije lijeve klijetke.[130]

Zatajivanje srca u bolesnika s karcinomom

Interes za kardioonkologiju odražava poboljšanje preživljavanja nakon liječenja karcinoma, rastuću osviještenosti o KV toksičnosti povezane s poznatim i novim onkološkim lijekobeen proposed. A small RCT suggested that empagliflozin stimulated production of erythropoietin leading to a rise in haematocrit and a fall in ferritin, a marker of inflammation and iron deficiency, although not transferrin saturation, a marker of iron deficiency alone.[117] However, administration of exogenous erythropoietin did not reduce morbidity or mortality in the RED-HF trial.[118] Others have suggested that SGLT2i increase the production of ketones, which may be a more efficient myocardial energy substrate, or block myocardial sodium–hydrogen exchanger-3, which may improve myocardial function and reduce fibrosis.[119,120]

An RCT of empagliflozin in patients with T2DM but not heart failure[121] suggested little effect on cardiac function or remodelling; RCTs of the effects of SGLT2i on cardiac function in patients with HFrEF and HFpEF are awaited. Future trials will confirm whether the benefit observed in DAPA-HF is a class effect and whether they are effective for HFpEF or when congestion is severe.[122,123]

Acute heart failure

Two large RCTs of serelaxin failed to confirm the results of the original RELAX-AHF trial. RELAX-AHF-EU,[124] an open-label RCT (n = 2688), reported a similar and low rate for mortality (≤2%) and re-admissions for heart failure (<1%) at 14 days for patients assigned placebo or serelaxin, despite a reduction in worsening heart failure at day 5 [6.7–4.5% (P < 0.008)]. The RELAX-AHF-2 trial,[125] a double-blind RCT (n = 6545), reported that the rates of worsening heart failure in the first 5 days (about 7%) and 180-day mortality (about 11%) were similar for placebo and serelaxin. The failure of so many short-term interventions for AHF may reflect failed therapeutic concepts, ineffective interventions, or problems with trial design. RCTs of AHF are difficult to implement, especially if conducted double-blind. Indeed, GALACTIC, a trial of personalized, early intensive and sustained vasodilation with nitrates and hydralazine, also failed to show benefit, calling into question the concept of vasodilator therapy for the routine management of acute heart failure.[126] Many patients present with acute breathlessness in the middle of the night. It is difficult to have research staff available '24/7' when there is no 'gateway' similar to a coronary care unit or catheter laboratory. Compassionate investigators may also be unwilling to enrol frail elderly patients who are most at risk of adverse outcomes. Moreover, breathlessness usually responds to oxygen and diuretics within hours,[127] especially for patients with a systolic blood pressure ≥125 mmHg, as required in the serelaxin trials. On the other hand, patients with extensive peripheral oedema,[26] renal dysfunction, and a low blood pressure, who often do not constitute an acute emergency have a poor prognosis and an unmet need for more effective interventions; pharmacological, or device.[127-129]

Stem cell therapy

Intra-myocardial injection of stem cells failed to improve weaning from left ventricular assist devices.[130]

Heart failure in patients with cancer

Interest in cardio-oncology reflects increasing survival after treatment for cancer, growing awareness of the CV toxicity associated with both established and new treatments for can-

vima te zanimanja za personaliziranu procjenu rizika prije kemoterapije. Ljudi s kardiomiopatijskom genskom mutacijom mogu biti podložniji (7,5 % onih s mutacijom gena tinin prema 1,1 % onih bez takve mutacije) razvoju disfunkcije klijetke nakon primjene kemoterapije.[131]

Prekid terapije trastuzumabom (oko 60 % prekida dogodi se zbog kardiotoksičnosti) povezan je s povećanim rizikom od recidiva karcinoma u žena s rano invazivnim HER2 pozitivnim karcinomom dojke.[132] Jedna opsevacijska studija pokazala je da se na svakih 30 žena koje su primale HER2 ciljanu terapiju i u kojih se LVEF smanjila na 40 – 49 %, a bile su prospektivno liječene beta-blokatorima i ACE inhibitorima, u njih samo tri razvio teški HF ili LVEF <35 %.[133] Funkcija srca malokad se vraća u normalu nakon dovršetka terapije, dovodeći u pitanje mišljenje da je trastuzumabom uzrokovana kardimiopatija obično reverzibilna. Novija je studija pokazala povećanu stopu CV događaja, posebno HF-a, među bolesnicima koji se liječe zbog multiplog mijeloma i primaju potentne inhibitore proteasoma, kao što su carfilzomib i bortezomid,[134] što je bilo povezano s mnogo lošijim preživljavanjem. Faktor rizika za razvoj CV događaja bila je povišena vrijednost NT-proBNP-a prije početka terapije ili porast tijekom liječenja. Sustavan pregled profilaktičnog uzimanja anatagonista renin-angiotenzin-aldosterona i beta-blokatora identificiralo je 22 relevantne randomizirane studije, od kojih je najveća uključivala samo 206 bolesnika[135,136], no nisu utvrđeni uvjerljivi dokazi kliničke učinkovitosti.

Implementacija terapije

Analiza administrativnih baza podataka primarne prakse u UK pokazuje da se implementacija terapije znatno poboljšala tijekom posljednjeg desetljeća, sa sada 72 % propisanih beta-blokatora, iako mnogi bolesnici ostaju na dozi manjoj od ciljne.[6] Među otpuštenima iz bolnica u Engleskoj i Walesu, 89 % bolesnika s HFrEF otpušteni su na beta-blokatoru (*https://www.nicor.org.uk/wp-content/uploads/2019/09/Heart-Failure-2019-Report-final.pdf*), što je vrlo slično onomu što je zapaženo u bolesnika s HFrEF-om koji su bili birani za uključenje u *ESC-EURObservational Heart Failure Long-Term Registry*.[137] Međutim, analiza podataka američkih korisnika *Medicare* utvrdila je da je samo 51 % bolesnika s HFrEF-om imalo propisan beta-blokator nakon prve ili ponavljajuće hospitalizacije i samo 12 % primalo je najmanje ≥50 % ciljne doze do jedne godine.[138] Ovo upućuje na to da organizacija skrbi kod HFrEF-a radi veliku razliku u liječenju te posljedično u ishodima. Međutim, randomizirana kontrolirana studijska skupina (n = 2494) usluga reorganiziranih u svrhu poboljšanja tranzicije s bolničkog liječenja na dolazak kući, što je uključivalo edukaciju o samopomoći, strukturirano otpusno pismo, dolazak k obiteljskom liječniku unutar tjedan dana i kućne posjete za visokorizične bolesnike, nije znatno pridonijelo tomu da se bolesnici bolje osjećaju ili utjecalo na ishode.[139] Jedna randomizirana studija (n = 110) pokazala je da česti (nekoliko puta mjesečno) odlasci na sudjelovanje u aktivnostima lokalnih ljekarni može popraviti adherenciju uzimanja lijekova i pridonijeti dobrom osjećanju.[140] Randomizirano istraživanje među 450 bolesnika utvrdilo je dobrobit *e-Health* intervencije na ponašanje u smislu samopomoći i kvalitete života u prva tri mjeseca nakon započinjanja, ali ne i nakon toga,[141] bez učinka na broj hospitalizacija ili mortalitet. Ima mnogo razloga zašto randomizirane studije složenih intervencija ne uspijevaju,

cer, and interest in personalized risk-profiling prior to chemotherapy. People with cardiomyopathy-related gene mutations may be more prone (7.5% of those with compared to 1.1% of those without a titin gene mutation) to develop ventricular dysfunction after the administration of chemotherapy.[131]

Interruption of trastuzumab is associated with a higher risk of cancer recurrence in women with early invasive HER2^{+ve} breast cancer; about 60% of interruptions are for cardiotoxicity.[132] An observational study showed that of 30 women receiving HER2-targeted therapies who developed an LVEF of 40–49% and were treated prospectively with beta-blockers and ACE inhibitors, only three went on to develop severe heart failure or a LVEF <35%.[133] Cardiac function rarely returned to normal after completion of treatment, challenging the view that trastuzumab-related LV dysfunction is usually reversible. A recent study reported high rates of CV events, especially heart failure, amongst patients with multiple myeloma receiving potent proteasome inhibitors, such as carfilzomib and bortezomib,[134] which were associated with much poorer survival. Risk factors for developing a CV event included elevated pre-treatment NT-proBNP or an increase during treatment. A systematic review of prophylactic use of renin–angiotensin–aldosterone antagonists and beta-blockers identified 22 relevant RCTs, of which the largest had only 206 patients,[135,136] but found no convincing evidence of clinical efficacy

Implementation of therapy

Analyses of administrative data from primary care in the UK suggest that implementation of therapy has improved substantially over the last decade, with 72% now prescribed a beta-blocker, although many patients remain on less than target doses.[6] Amongst hospital discharges in England and Wales, 89% of those with HFrEF were discharged on a beta-blocker (*https://www.nicor.org.uk/wp-content/uploads/2019/09/Heart-Failure-2019-Report-final.pdf*), which is very similar to that observed in patients with HFrEF selected for enrolment in the ESC-EURObservational Heart Failure Long-Term Registry.[137] However, an analysis of Medicare beneficiaries in the USA found that only 51% of patients with HFrEF were prescribed a beta-blocker after a first or recurrent hospitalization for heart failure and only 12% received at least ≥50% of the target dose by 1 year.[138] This suggests that the organization of care for HFrEF makes an important difference to treatment and, consequently, outcome. However, a cluster RCT (n = 2494) of service redesign aiming to improve hospital-to-home transition, which included self-care education, a structured hospital discharge summary, family physician follow-up within 1 week, and, for high-risk patients, home-visits, did not substantially improve patient well-being or outcome.[139] An RCT (n = 110) showed that frequent (several times per month) visits to participating community pharmacies could improve medication adherence and well-being.[140] An RCT of 450 patients found benefits of e-Health intervention on self-care behaviour and quality of life in the first 3 months after initiation but not thereafter,[141] with no effect on hospitalizations or mortality. There are many reasons why RCTs of complex interventions fail including inadequate power, suboptimal trial design, already excellent or unintended improvements in care for the control group, lack of long-term engagement and motivation of staff and patients, inclusion of patients for whom pharmacological intervention is largely ineffective (e.g. HFpEF) but sometimes we just have to admit that what should work does not. More evidence is required; learning from past experience.[142]

uključujući neadekvatnu snagu, suboptimalni dizajn studije, već jako dobra ili nehotično poboljšana skrb kontrolne grupe, manjak dugotrajnog angažiranosti osoblja i bolesnika, uključivanje bolesnika u kojih je farmakološka intervencija uglavnom neučinkovita (npr. HFpEF), ali pokatkad moramo priznati da nešto što bi trebalo biti uspješno ne pokazuje učinak. Potrebno je više dokaza te učenja iz prošlih iskustava.[142]

Rehabilitacija

Sistematski pregledi upućuju na to da rehabilitacija temeljena na vježbanju može poboljšati bolesnikov osjećaj dobrog stanja i kapacitet vježbanja, smanjiti zatajivanjem srca uzrokovane, ali i sve ostale hospitalizacije, ali ne može smanjiti mortalitet, usprkos potencijalnom poboljšanju adherencije liječenja.[143-147] Najbolji i najisplativiji način provođenja tema je aktivnih istraživanja.[148,149]

Palijativna skrb

Morfij olakšava kronični nedostatak zraka u bolesnika s kroničnim bolestima pluća, ali podatci za HF su oskudni. Randomizirana studija među 45 bolesnika nije uspjela dokazati značajnu kliničku korist od morfija primijenjenog u bolesnika s HFrEF-om ili HFpEF-om, dominantno u NYHA III. funkcionalnoj skupini.[150]

Ukidanje terapije za zatajivanje srca nakon oporavka

Ukidanje terapije u bolesnika s idiopatskom ili genski uzrokovanom dilatativnom kardiomiopatijom koji su postigli puni oporavak ventrikularne funkcije trebalo bi se učiniti s velikom pažnjom.[151] Iako bolesnici s oporavljenom LVEF (HFrcEF) mogu imati bolju prognozu, to još uvijek ne mora biti dobro.[152] Potrebna su dodatna istraživanja za peripartalnu i druge specifične vrste kardiomiopatija. Noviji izvještaj iz jedne stare studije (*DIG*) pokazao je da je ukidanje digoksina bilo povezano s povećanim rizikom od hospitalizacija zbog HF-a, ali nije utjecalo na mortalitet.[153] Randomizirano istraživanje koje je uključilo 188 bolesnika sa stabilnim HF-om iz Brazila pokazalo je da se u 75 % bolesnika može ukinuti diuretik Henleove petlje na najmanje 90 dana bez pogoršanja simptoma, potrebe za ponovnim uvođenjem diuretske terapije ili porasta plazmatskog NT-proBNP-a.[154] To je u velikoj suprotnosti s manjom randomiziranom studijom iz UK, u kojoj je ukidanje diuretika i drugih lijekova kroz 48 h uzrokovalo dvostruk porast vrijednosti NT-proBNP-a, povećanje volumena LV-a i lijevog atrija i pogoršanje simptoma.[155]

Zaključak

Tijekom prošle godine postignut je velik napredak u razumijevanju i liječenju HF-a. Nove kontroverze i novi dokazi dovode u kušnju mnoge stare pretpostavke. Kao i uvijek, neki će se odupirati napretku, a drugi će ga prigrliti. Vi, čitatelju, morate pomoći našoj profesiji i bolesniku i pronaći pravu ravnotežu između nesmotrenog entuzijazma i dijagnostičke i terapijske inercije.

Rehabilitation

Systematic reviews suggest that exercise-based rehabilitation can improve patients' well-being and exercise capacity and reduce heart failure-related and all-cause hospitalization but may not reduce mortality, despite potentially improving adherence to treatment.[143–147] The best and most cost-effective service-model is a topic of active research.[148,149]

Palliative care

Morphine relieves chronic breathlessness in patients with chronic lung disease but data for heart failure are sparse. An RCT of 45 patients failed to demonstrate important clinical benefits of morphine administration to patients with HFrEF or HFpEF predominantly in NYHA functional class III.[150]

Withdrawing treatment for heart failure after recovery

Withdrawing treatment from patients with idiopathic or genetically determined dilated cardiomyopathy who have experienced full recovery of ventricular function should be done with great caution if at all.[151] Although patients with a recovered LVEF (HFrcEF) may have a better prognosis, it may still not be good.[152] Further research is required for peripartum and other specific types of cardiomyopathy. A recent report from an old trial (DIG), suggested that withdrawal of digoxin was associated with an increased risk of hospitalization for heart failure but did not affect mortality.[153] An RCT of 188 patients with stable heart failure from Brazil suggested that 75% of patients could be withdrawn from loop diuretics for at least 90 days without deterioration in symptoms, need for reinstitution of diuretic therapy, or a rise in plasma NT-proBNP.[154] This is in stark contrast to a smaller RCT from the UK, where withdrawal of diuretics and other therapies for 48 h led to a doubling of plasma concentrations of NT-proBNP, an increase in LV and left atrial volumes and worsening symptoms.[155]

Conclusion

Great progress in the understanding and management of heart failure has been made over the last year. New controversies and new evidence challenge many old assumptions. As ever, some will resist progress and others will embrace it. You, the reader, must help our professions and patients find the correct balance between reckless enthusiasm and diagnostic and therapeutic inertia.

Funding

The British Heart Foundation Cardiovascular Research Centre at the University of Glasgow is supported by a Centre of Research Excellence grant from the British Heart Foundation (RE/18/6/34217).

Conflict of interest: Dr J.G.C. reports grants and personal fees from Amgen, Bayer, Novartis, Vifor, and Pharmacosmos; personal fees and non-financial support from Medtronic; personal fees from Abbott, outside the submitted work. Dr A.R.L. reports personal fees from Servier, Novartis, Roche, Takeda, Boehringer Ingelheim, Amgen, Clinigen Group, Ferring Pharmaceuticals, Eli Lily, Bristol Myers Squibb, and Eisai Ltd; grants and personal fees from Pfizer, outside the submitted work. T.M. reports honoraria from Vifor. J.J.M. reports non-financial support and other from AstraZeneca, during the conduct of the study; other from Bayer, non-financial support and other from Cardiorentis, non-financial support and other from Amgen, non-financial support and other from Oxford University/Bayer, non-financial support and other from Theracos, non-financial support and other from Abbvie, other from DalCor, other from Pfizer, other from Merck, non-financial support and other from Novartis, non-financial support and other from Glaxo Smith Kline (GSK), other from Bristol Myers Squibb (BMS), non-financial support and other from Vifor-Fresenius, non-financial support and other from Kidney Research UK (KRUK), non-financial support and other from Novartis, outside the submitted work.

LITERATURE

1. Torabi A, Rigby AS, Cleland J. Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. J Am Coll Cardiol. 2009;55:79-81. https://doi.org/10.1016/j.jacc.2009.05.080
2. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation. 2014;130:1579-88. https://doi.org/10.1161/CIRCULATIONAHA.114.010389
3. Zhang C, Jiang L, Xu L, Tian J, Liu J, Zhao X, et al. Implications of N-terminal pro-B-type natriuretic peptide in patients with three-vessel disease. Eur Heart J. 2019;40:3397-405. https://doi.org/10.1093/eurheartj/ehz394
4. Cleland JGF, Pellicori P, Clark AL. Prevention or procrastination for heart failure? Why we need a universal definition of heart failure. J Am Coll Cardiol. 2019;73:2398-400. https://doi.org/10.1016/j.jacc.2019.03.471
5. Conrad N, Judge A, Canoy D, Tran J, Pinho-Gomes AC, Millett ERC, et al. Temporal trends and patterns in mortality after incident heart failure: a longitudinal analysis of 86000 individuals. JAMA Cardiol. 2019;4:1102. https://doi.org/10.1001/jamacardio.2019.3593
6. Conrad N, Judge A, Canoy D, Tran J, O'Donnell J, Nazarzadeh M, et al. Diagnostic tests, drug prescriptions, and follow-up patterns after incident heart failure: a cohort study of 93,000 UK patients. PLoS Med. 2019;16:e1002805. https://doi.org/10.1371/journal.pmed.1002805
7. Bottle A, Kim D, Aylin P, Cowie MR, Majeed A, Hayhoe B. Routes to diagnosis of heart failure: observational study using linked data in England. Heart. 2018;104:600-5. https://doi.org/10.1136/heartjnl-2017-312183
8. Kim D, Hayhoe B, Aylin P, Majeed A, Cowie MR, Bottle A. Route to heart failure diagnosis in English primary care: a retrospective cohort study of variation. Br J Gen Pract. 2019;69:e697-705. https://doi.org/10.3399/bjgp19X705485
9. Filippatos G, Angermann CE, Cleland JGF, Lam CSP, Dahlström U, Dickstein K, et al. Global differences in acute heart failure patient characteristics, precipitants, point of hospital entry and inpatient management: an analysis from REPORT-HF, a worldwide, prospective heart failure disease registry. JAMA Cardiol. 2020 Jan 8;5(4):401-410. https://doi.org/10.1001/jamacardio.2019.5108
10. Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, et al. INTER-CHF Investigators. Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. Lancet Glob Health. 2017;5:e665-72. https://doi.org/10.1016/S2214-109X(17)30196-1
11. Dewan P, Rorth R, Jhund PS, Ferreira JP, Zannad F, Shen L, et al. Income inequality and outcomes in heart failure: a global between-country analysis. JACC Heart Fail. 2019;7:336-46. https://doi.org/10.1016/j.jchf.2018.11.005
12. Dewan P, Jhund PS, Shen L, Petrie MC, Abraham WT, Atif AM, et al. Sibulo ASJr, Solomon SD, Sritara P, Swedberg K, Tsutsui H, Zile MR, McMurray J. Heart failure with reduced ejection fraction: comparison of patient characteristics and clinical outcomes within Asia and between Asia, Europe and the Americas. Eur J Heart Fail. 2019;21:577-87. https://doi.org/10.1002/ejhf.1347
13. Ferreira JP, Rossello X, Eschalier R, McMurray JJV, Pocock S, Girerd N, et al. MRAs in elderly HF patients: individual patient-data meta-analysis of RALES, EMPAHSIS-HF, and TOPCAT. JACC Heart Fail. 2019;7:1012-21. https://doi.org/10.1016/j.jchf.2019.08.017
14. Ferreira JP, Rossignol P, Pizard A, Machu JL, Collier T, Girerd N, et al. Potential spironolactone effects on collagen metabolism biomarkers in patients with uncontrolled blood pressure. Heart. 2019;105:307-14. https://doi.org/10.1136/heartjnl-2018-313182
15. Pellicori P, Ferreira JP, Mariottoni B, Brunner-La Rocca H-P, Ahmed FZ, Verdonschot J, et al. Effects of spironolactone on serum markers of fibrosis in people at high risk of developing heart failure: rationale, design and baseline characteristics of a proof-of-concept, randomised, precision-medicine, prevention trial. The Heart OMics in AGing (HOMAGE) trial. Eur J Heart Fail. 2020 Jan 16. doi: 10.1002/ejhf.1716. Online ahead of print.
16. Larsson SC, Back M, Rees JMB, Mason AM, Burgess S. Body mass index and body composition in relation to 14 cardiovascular conditions in UK Biobank: a Mendelian randomization study. Eur Heart J. 2020 Jan 7;41(2):221-226. https://doi.org/10.1093/eurheartj/ehz388
17. Sillars A, Celis-Morales CA, Ho FK, Petermann F, Welsh P, Iliodromiti S, et al. Association of fitness and grip strength with heart failure: findings from the UK biobank population-based study. Mayo Clin Proc. 2019;94:2230-40. https://doi.org/10.1016/j.mayocp.2019.04.041
18. Jamaly S, Carlsson L, Peltonen M, Jacobson P, Karason K. Surgical obesity treatment and the risk of heart failure. Eur Heart J. 2019;40:2131-8. https://doi.org/10.1093/eurheartj/ehz295
19. Zhang J, Begley A, Jackson R, Harrison M, Pellicori P, Clark AL, et al. Body mass index and all-cause mortality in heart failure patients with normal and reduced ventricular ejection fraction: a dose-response meta-analysis. Clin Res Cardiol. 2019;108:119-32. https://doi.org/10.1007/s00392-018-1302-7
20. Kytömaa S, Hegde S, Claggett B, Udell JA, Rosamond W, Temte J, et al. Association of influenza-like illness activity with hospitalizations for heart failure: the atherosclerosis risk in communities study. JAMA Cardiol. 2019;4:363-9. https://doi.org/10.1001/jamacardio.2019.0549
21. Loeb M, Dokainish H, Dans A, Palileo-Villanueva LM, Roy A, Karaye K, et al. Randomized controlled trial of influenza vaccine in patients with heart failure to reduce adverse vascular events (IVVE): rationale and design. Am Heart J. 2019;212:36-44. https://doi.org/10.1016/j.ahj.2019.02.009
22. Liu L, Klein L, Eaton C, Panjrath G, Martin LW, Chae CU, et al. Menopausal hormone therapy and risks of first hospitalized heart failure and its subtypes during the intervention and extended postintervention follow-up of the women's health initiative randomized trials. J Card Fail. 2020 Jan;26(1):2-12. https://doi.org/10.1016/j.cardfail.2019.09.006
23. Pieske B, Tschope C, de Boer RA, Fraser AG, Anker SD, Donal E, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40:3297-317. https://doi.org/10.1093/eurheartj/ehz641
24. Ho JE, Zern EK, Wooster L, Bailey CS, Cunningham T, Eisman AS, et al. Differential clinical profiles, exercise responses, and outcomes associated with existing HFpEF definitions. Circulation. 2019;140:353-65. https://doi.org/10.1161/CIRCULATIONAHA.118.039136
25. Pellicori P, Shah P, Cuthbert J, Urbinati A, Zhang J, Kallvikbacka-Bennett A, et al. Prevalence, pattern and clinical relevance of ultrasound indices of congestion in outpatients with heart failure. Eur J Heart Fail. 2019;21:904-16. https://doi.org/10.1002/ejhf.1383
26. Shoaib A, Mamas MA, Ahmad QS, McDonagh TM, Hardman SMC, Rashid M, et al. Characteristics and outcome of acute heart failure patients according to the severity of peripheral oedema. Int J Cardiol. 2019;285:40-6. https://doi.org/10.1016/j.ijcard.2019.03.020
27. Shoaib A, Farag M, Nolan J, Rigby A, Patwala A, Rashid M, et al. Mode of presentation and mortality amongst patients hospitalized with heart failure? A report from the First Euro Heart Failure Survey. Clin Res Cardiol. 2019;108:510-9. https://doi.org/10.1007/s00392-018-1380-6
28. Platz E, Solomon SD, McMurray J. Lung ultrasound: monitoring congestion in patients with heart failure. Eur J Heart Fail. 2019 Dec;21(12):1614-1615. https://doi.org/10.1002/ejhf.1636
29. Platz E, Campbell RT, Claggett B, Lewis EF, Groarke JD, Docherty KF, et al. Lung ultrasound in acute heart failure: prevalence of pulmonary congestion and short- and long-term outcomes. JACC Heart Fail. 2019;7:849-58. https://doi.org/10.1016/j.jchf.2019.07.008
30. Platz E, Jhund PS, Girerd N, Pivetta E, McMurray JJV, Peacock WF, et al.; on behalf of the Study Group on Acute Heart Failure of the Acute Cardiovascular Care Association and the Heart Failure Association of the European Society of Cardiology. Expert consensus document: reporting checklist for quantification of pulmonary congestion by lung ultrasound in heart failure. Eur J Heart Fail. 2019;21:844-51. https://doi.org/10.1002/ejhf.1499
31. Pivetta E, Goffi A, Nazerian P, Castagno D, Tozzetti C, Tizzani P, et al.; on behalf of the Study Group on Lung Ultrasound from the Molinette and Careggi Hospitals. Lung ultrasound integrated with clinical assessment for the diagnosis of acute decompensated heart failure in the emergency department: a randomized controlled trial. Eur J Heart Fail. 2019;21:754-66. https://doi.org/10.1002/ejhf.1379

32. Rivas-Lasarte M, Álvarez-García J, Fernández-Martínez J, Maestro A, López-López L, Solé-González E, et al. Lung ultrasound-guided treatment in ambulatory patients with heart failure: a randomized controlled clinical trial (LUS-HF study). Eur J Heart Fail. 2019 Dec;21(12):1605-1613. https://doi.org/10.1002/ejhf.1604

33. Ter Maaten JM, Kremer D, Demissei BG, Struck J, Bergmann A, Anker SD, et al. Bio-adrenomedullin as a marker of congestion in patients with new-onset and worsening heart failure. Eur J Heart Fail. 2019;21:732–43. https://doi.org/10.1002/ejhf.1437

34. Abraham J, Bharmi R, Jonsson O, Oliveira GH, Artis A, Valika A, et al. Association of ambulatory hemodynamic monitoring of heart failure with clinical outcomes in a concurrent matched cohort analysis. JAMA Cardiol. 2019;4:556–63. https://doi.org/10.1001/jamacardio.2019.1384

35. Verbrugge FH, Martens P, Ameloot K, Haemels V, Penders J, Dupont M, et al. Acetazolamide to increase natriuresis in congestive heart failure at high risk for diuretic resistance. Eur J Heart Fail. 2019;21:1415–22. https://doi.org/10.1002/ejhf.1478

36. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail. 2019;21:1306–25. https://doi.org/10.1002/ejhf.1594

37. Kwok CS, Zieroth S, Van Spall HGC, Helliwell T, Clarson L, Mohamed M, et al. The Hospital Frailty Risk Score and its association with in-hospital mortality, cost, length of stay and discharge location in patients with heart failure short running title: frailty and outcomes in heart failure. Int J Cardiol. 2020 Feb 1;300:184-190. https://doi.org/10.1016/j.ijcard.2019.09.064

38. Savarese G, Dahlstrom U, Vasko P, Pitt B, Lund LH. Association between renin-angiotensin system inhibitor use and mortality/morbidity in elderly patients with heart failure with reduced ejection fraction: a prospective propensity score-matched cohort study. Eur Heart J. 2018;39:4257–65. https://doi.org/10.1093/eurheartj/ehy621

39. Stolfo D, Uijl A, Benson L, Schrage B, Fudim M, Asselbergs FW, et al. Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction. A propensity score-matched analysis from the Swedish Heart Failure Registry. Eur J Heart Fail. 2020 Jan;22(1):103-112. https://doi.org/10.1002/ejhf.1615

40. Rush CJ, Campbell RT, Jhund PS, Petrie MC, McMurray J. Association is not causation: treatment effects cannot be estimated from observational data in heart failure. Eur Heart J. 2018;39:3417–38. https://doi.org/10.1093/eurheartj/ehy407

41. Triposkiadis F, Butler J, Abboud FM, Armstrong PW, Adamopoulos S, Atherton JJ, et al. The continuous heart failure spectrum: moving beyond an ejection fraction classification. Eur Heart J. 2019;40:2155–63. https://doi.org/10.1093/eurheartj/ehz158

42. de Boer RA, De KG, Bauersachs J, Brutsaert D, Cleland JG, Diez J, et al. Towards better definition, quantification and treatment of fibrosis in heart failure. A scientific roadmap by the Committee of Translational Research of the Heart Failure Association (HFA) of the European Society of Cardiology. Eur J Heart Fail. 2019;21:272–85. https://doi.org/10.1002/ejhf.1406

43. Packer M. The epicardial adipose inflammatory triad: coronary atherosclerosis, atrial fibrillation, and heart failure with a preserved ejection fraction. Eur J Heart Fail. 2018;20:1567–9. https://doi.org/10.1002/ejhf.1294

44. Pellicori P, Zhang J, Cuthbert J, Urbinati A, Shah P, Kazmi S, et al. High sensitivity C-reactive protein in chronic heart failure: patient characteristics, phenotypes and mode of death. Cardiovasc Res. 2020;116:91–100. https://doi.org/10.1093/cvr/cvz198

45. Tromp J, Ouwerkerk W, Demissei BG, Anker SD, Cleland JG, Dickstein K, et al. Novel endotypes in heart failure: effects on guideline-directed medical therapy. Eur Heart J. 2018;39:4269–76. https://doi.org/10.1093/eurheartj/ehy712

46. Kao DP, Lewsey JD, Anand IS, Massie BM, Zile MR, Carson PE, et al. Characterization of subgroups of heart failure patients with preserved ejection fraction with possible implications for prognosis and treatment response. Eur J Heart Fail. 2015;17:925–35. https://doi.org/10.1002/ejhf.327

47. Cao TH, Jones DJL, Voors AA, Quinn PA, Sandhu JK, Chan DCS, et al. Plasma proteomic approach in patients with heart failure: insights into pathogenesis of disease progression and potential novel treatment targets. Eur J Heart Fail. 2020 Jan;22(1):70-80. https://doi.org/10.1002/ejhf.1608

48. Cleland JGF, Van Veldhuisen DJ, Ponikowski P. The year in cardiology 2018: heart failure. Eur Heart J. 2019;40:651–61. https://doi.org/10.1093/eurheartj/ehz010

49. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129–200. https://doi.org/10.1093/eurheartj/ehw128

50. Wehner GJ, Jing L, Haggerty CM, Suever JD, Leader JB, Hartzel DN, et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? Eur Heart J. 2020 Mar 21;41(12):1249-1257. https://doi.org/10.1093/eurheartj/ehz550

51. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of The Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019;21:1169–86. https://doi.org/10.1002/ejhf.1531

52. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. Eur Heart J. 2019;40:689–97. https://doi.org/10.1093/eurheartj/ehy809

53. Pellicori P, Urbinati A, Kaur K, Zhang J, Shah P, Kazmi S, et al. Prevalence and incidence of atrial fibrillation in ambulatory patients with heart failure. Am J Cardiol. 2019;124:1554–60. https://doi.org/10.1016/j.amjcard.2019.08.018

54. Anderson SG, Shoaib A, Myint PK, Cleland JG, Hardman SM, McDonagh TA, et al. Does rhythm matter in acute heart failure? An insight from the British Society for Heart Failure National Audit. Clin Res Cardiol. 2019;108:1276–86. https://doi.org/10.1007/s00392-019-01463-5

55. Packer M. Effect of catheter ablation on pre-existing abnormalities of left atrial systolic, diastolic, and neurohormonal functions in patients with chronic heart failure and atrial fibrillation. Eur Heart J. 2019;40:1873–9. https://doi.org/10.1093/eurheartj/ehz284

56. Chen S, Purerfellner H, Meyer C, Acou WJ, Schratter A, Ling Z, et al. Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. Eur Heart J. 2019 Jul 11;ehz443. doi: 10.1093/eurheartj/ehz443. Online ahead of print.

57. Barra S, Duehmke R, Providencia R, Narayanan K, Reitan C, Roubicek T, et al. Very long-term survival and late sudden cardiac death in cardiac resynchronization therapy patients. Eur Heart J. 2019;40:2121–7. https://doi.org/10.1093/eurheartj/ehz238

58. Barra S, Providencia R, Narayanan K, Boveda S, Duehmke R, Garcia R, et al. Time trends in sudden cardiac death risk in heart failure patients with cardiac resynchronization therapy: a systematic review. Eur Heart J. 2020 Jun 1;41(21):1976-1986. https://doi.org/10.1093/eurheartj/ehz238

59. Cleland JGF, Hindricks G, Petrie M. The shocking lack of evidence for implantable cardioverter defibrillators for heart failure; with or without cardiac resynchronization. Eur Heart J. 2019;40:2128–30. https://doi.org/10.1093/eurheartj/ehz409

60. Halliday BP, Baksi AJ, Gulati A, Ali A, Newsome S, Izgi C, et al. Outcome in dilated cardiomyopathy related to the extent, location, and pattern of late gadolinium enhancement. JACC Cardiovasc Imaging. 2019;12:1645–55. https://doi.org/10.1016/j.jcmg.2018.07.015

61. Rørth R, Dewan P, Kristensen SL, Jhund PS, Petrie MC, Kober L, et al. Efficacy of an implantable cardioverter-defibrillator in patients with diabetes and heart failure and reduced ejection fraction. Clin Res Cardiol. 2019;108:868–77. https://doi.org/10.1007/s00392-019-01415-z

62. Rossello X, Ariti C, Pocock SJ, Ferreira JP, Girerd N, McMurray JJV, et al. Impact of mineralocorticoid receptor antagonists on the risk of sudden cardiac death in patients with heart failure and left-ventricular systolic dysfunction: an individual patient-level meta-analysis of three randomized-controlled trials. Clin Res Cardiol. 2019;108:477-86. https://doi.org/10.1007/s00392-018-1378-0
63. Nikolaidou T, Johnson MJ, Ghosh JM, Marincowitz C, Shah S, Lammiman MJ, et al. Postmortem ICD interrogation in mode of death classification. J Cardiovasc Electrophysiol. 2018;29:573-83. https://doi.org/10.1111/jce.13414
64. Leclercq C, Burri H, Curnis A, Delnoy PP, Rinaldi CA, Sperzel J, et al. Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from Phase I. Eur Heart J. 2019;40:2979-87. https://doi.org/10.1093/eurheartj/ehz109
65. Asch FM, Grayburn PA, Siegel RJ, Kar S, Lim DS, Zaroff JG, et al. Echocardiographic outcomes after transcatheter leaflet approximation in patients with secondary mitral regurgitation: the COAPT trial. J Am Coll Cardiol. 2019;74:2969-79. https://doi.org/10.1016/j.jacc.2019.09.017
66. Baron SJ, Wang K, Arnold SV, Magnuson EA, Whisenant B, Brieke A, et al.; On behalf of the COAPT Investigators. Cost-effectiveness of transcatheter mitral valve repair versus medical therapy in patients with heart failure and secondary mitral regurgitation: results from the COAPT trial. Circulation. 2019;140:1881-91. https://doi.org/10.1161/CIRCULATIONAHA.119.043275
67. Arnold SV, Chinnakondepalli KM, Spertus JA, Magnuson EA, Baron SJ, Kar S, et al. Health status after transcatheter mitral-valve repair in heart failure and secondary mitral regurgitation: COAPT trial. J Am Coll Cardiol. 2019;73:2123-32. https://doi.org/10.1016/j.jacc.2019.02.010
68. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med. 2018;379:2307-18. https://doi.org/10.1056/NEJMoa1806640
69. Iung B, Armoiry X, Vahanian A, Boutitie F, Mewton N, Trochu JN, et al.; on behalf of the MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years. Eur J Heart Fail. 2019 Dec;21(12):1619-1627. https://doi.org/10.1002/ejhf.1616
70. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. JACC Cardiovasc Imaging. 2019;12:353-62. https://doi.org/10.1016/j.jcmg.2018.11.006
71. Packer M, Grayburn PA. Contrasting effects of pharmacological, procedural, and surgical interventions on proportionate and disproportionate functional mitral regurgitation in chronic heart failure. Circulation. 2019;140:779-89. https://doi.org/10.1161/CIRCULATIONAHA.119.039612
72. Witte KK, Lipiecki J, Siminiak T, Meredith IT, Malkin CJ, Goldberg SL, et al. The REDUCE FMR trial: a randomized sham-controlled study of percutaneous mitral annuloplasty in functional mitral regurgitation. JACC Heart Fail. 2019;7:945-55. https://doi.org/10.1016/j.jchf.2019.06.011
73. Nickenig G, Weber M, Lurz P, von Bardeleben RS, Sitges M, Sorajja P, et al. Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study. Lancet. 2019;394:2002-11. https://doi.org/10.1016/S0140-6736(19)32600-5
74. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, et al. Transcatheter versus medical treatment of symptomatic severe tricuspid regurgitation. J Am Coll Cardiol. 2019;74:2998-3008. https://doi.org/10.1016/j.jacc.2019.09.028
75. Branch KR, Probstfield JL, Eikelboom JW, Bosch J, Maggioni AP, Cheng RK, et al. Rivaroxaban with or without aspirin in patients with heart failure and chronic coronary or peripheral artery disease: the COMPASS trial. Circulation. 2019;140:529-37. https://doi.org/10.1161/CIRCULATIONAHA.119.039609
76. Cleland JGF, Pellicori P. Myocardial dysfunction and coronary artery disease as therapeutic targets in heart failure. Circulation. 2019;140:538-41. https://doi.org/10.1161/CIRCULATIONAHA.119.041523
77. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993-1004. https://doi.org/10.1056/NEJMoa1409077
78. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al.; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381:1995-2008. https://doi.org/10.1056/NEJMoa1911303
79. Greenberg B, Neaton JD, Anker SD, Byra WM, Cleland JGF, Deng H, et al. Association of rivaroxaban with thromboembolic events in patients with heart failure, coronary disease, and sinus rhythm: a post hoc analysis of the COMMANDER HF trial. JAMA Cardiol. 2019;4:515. https://doi.org/10.1001/jamacardio.2019.1049
80. Mehra MR, Vaduganathan M, Fu M, Ferreira JP, Anker SD, Cleland JGF, et al. A comprehensive analysis of the effects of rivaroxaban on stroke or transient ischaemic attack in patients with heart failure, coronary artery disease, and sinus rhythm: the COMMANDER HF trial. Eur Heart J. 2019;40:3593-602. https://doi.org/10.1093/eurheartj/ehz427
81. Morrow DA, Velazquez EJ, DeVore AD, Prescott MF, Duffy CI, Gurmu Y, et al. Cardiovascular biomarkers in patients with acute decompensated heart failure randomized to sacubitril-valsartan or enalapril in the PIONEER-HF trial. Eur Heart J. 2019;40:3345-52. https://doi.org/10.1093/eurheartj/ehz240
82. Wachter R, Senni M, Belohlavek J, Straburzynska-Migaj E, Witte KK, Kobalava Z, et al. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail. 2019;21:998-1007. https://doi.org/10.1002/ejhf.1498
83. Desai AS, Solomon SD, Shah AM, Claggett BL, Fang JC, Izzo J, et al. Effect of sacubitril-valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2019 Sep 2;322(11):1-10. https://doi.org/10.1001/jama.2019.12843
84. Januzzi JL Jr, Prescott MF, Butler J, Felker GM, Maisel AS, McCague K, et al. Association of change in N-terminal pro-B-type natriuretic peptide following initiation of sacubitril-valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA. 2019 Sep 2;322(11):1-11. https://doi.org/10.1001/jama.2019.12821
85. Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. Circulation. 2019;139:1354-65. https://doi.org/10.1161/CIRCULATIONAHA.118.037077
86. Zile MR, O'Meara E, Claggett B, Prescott MF, Solomon SD, Swedberg K, et al. Effects of sacubitril/valsartan on biomarkers of extracellular matrix regulation in patients with HFrEF. J Am Coll Cardiol. 2019;73:795-806. https://doi.org/10.1016/j.jacc.2018.11.042
87. Krum H, Elsik M, Schneider HG, Ptaszynska A, Black M, Carson PE, et al. Relation of peripheral collagen markers to death and hospitalization in patients with heart failure and preserved ejection fraction: results of the I-PRESERVE collagen substudy. Circ Heart Fail. 2011;4:561-8. https://doi.org/10.1161/CIRCHEARTFAILURE.110.960716
88. Solomon SD, Rizkala AR, Lefkowitz MP, Shi VC, Gong J, Anavekar N, et al. Baseline characteristics of patients with heart failure and preserved ejection fraction in the PARAGON-HF trial. Circ Heart Fail. 2018;11:e004962. https://doi.org/10.1161/circheartfailure.118.004962
89. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; on behalf of PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27:2338-45. https://doi.org/10.1093/eurheartj/ehl250
90. Parthasarathy HK, Pieske B, Weisskopf M, Andrews CD, Brunel P, Struthers AD, et al. A randomized, double-blind, placebo-controlled study to determine the effects of valsartan on exercise time in patients with symptomatic heart failure with preserved ejection fraction. Eur J Heart Fail. 2009;11:980-9. https://doi.org/10.1093/eurjhf/hfp120
91. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381:1609-20. https://doi.org/10.1056/NEJMoa1908655
92. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, et al. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887-98. https://doi.org/10.1056/NEJMoa0801369

93. Solomon SD, Vaduganathan M, Claggett BL, Packer M, Zile M, Swedberg K, et al. Sacubitril/valsartan across the spectrum of ejection fraction in heart failure. Circulation. 2020 Feb 4;141(5):352-361. https://doi.org/10.1161/circulationaha.119.044586

94. McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, et al. Effects of sacubitril-valsartan, versus valsartan, in women compared to men with heart failure and preserved ejection fraction: insights from PARAGON-HF. Circulation. 2020 Feb 4;141(5):338-351. https://doi.org/10.1161/circulationaha.119.044491

95. Vaduganathan M, Claggett BL, Desai AS, Anker SD, Perrone SV, Janssens S, et al. Prior heart failure hospitalization, clinical outcomes, and response to sacubitril/valsartan compared with valsartan in HFpEF. J Am Coll Cardiol. 2020 Jan 28;75(3):245-254. https://doi.org/10.1016/j.jacc.2019.11.003

96. Dewan P, Rorth R, Jhund PS, Shen L, Raparelli V, Petrie MC, et al. Differential impact of heart failure with reduced ejection fraction on men and women. J Am Coll Cardiol. 2019;73:29-40. https://doi.org/10.1016/j.jacc.2018.09.081

97. Chandra A, Vaduganathan M, Lewis EF, Claggett BL, Rizkala AR, Wang W, et al. Health-related quality of life in heart failure with preserved ejection fraction: the PARAGON-HF trial. JACC Heart Fail. 2019;7:862-74. https://doi.org/10.1016/j.jchf.2019.05.015

98. Santema BT, Ouwerkerk W, Tromp J, Sama IE, Ravera A, Regitz-Zagrosek V, et al. Identifying optimal doses of heart failure medications in men compared with women: a prospective, observational, cohort study. Lancet. 2019;394:1254-63. https://doi.org/10.1016/S0140-6736(19)31792-1

99. Merrill M, Sweitzer NK, Lindenfeld J, Kao DP. Sex differences in outcomes and responses to spironolactone in heart failure with preserved ejection fraction: a secondary analysis of TOPCAT trial. JACC Heart Fail. 2019;7:228-38. https://doi.org/10.1016/j.jchf.2019.01.003

100. Linde C, Cleland JGF, Gold MR, Claude DJ, Tang ASL, Young JB, et al. The interaction of sex, height, and QRS duration on the effects of cardiac resynchronization therapy on morbidity and mortality: an individual-patient data meta-analysis. Eur J Heart Fail. 2018;20:780-91. https://doi.org/10.1002/ejhf.1133

101. Eickhoff MK, Dekkers CCJ, Kramers BJ, Laverman GD, Frimodt-Moller M, Jorgensen NR, et al. Effects of dapagliflozin on volume status when added to renin-angiotensin system inhibitors. J Clin Med. 2019;8:E779. https://doi.org/10.3390/jcm8060779

102. Dekkers CCJ, Sjostrom CD, Greasley PJ, Cain V, Boulton DW, Heerspink H. Effects of the sodium-glucose co-transporter-2 inhibitor dapagliflozin on estimated plasma volume in patients with type 2 diabetes. Diabetes Obes Metab. 2019;21:2667-73. https://doi.org/10.1111/dom.13855

103. Cefalo CMA, Cinti F, Moffa S, Impronta F, Sorice GP, Mezza T, et al. Sotagliflozin, the first dual SGLT inhibitor: current outlook and perspectives. Cardiovasc Diabetol. 2019;18:20. https://doi.org/10.1186/s12933-019-0828-y

104. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117-28. https://doi.org/10.1056/NEJMoa1504720

105. Yang DY, He X, Liang HW, Zhang SZ, Zhong XB, Luo CF, et al. Comparative outcomes of heart failure among existent classes of anti-diabetic agents: a network meta-analysis of 171, 253 participants from 91 randomized controlled trials. Cardiovasc Diabetol. 2019;18:47. https://doi.org/10.1186/s12933-019-0853-x

106. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation. 2019;139:2022-31. https://doi.org/10.1161/CIRCULATIONAHA.118.038868

107. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019;7:776-85. https://doi.org/10.1016/S2213-8587(19)30249-9

108. Shen L, Rorth R, Cosmi D, Kristensen SL, Petrie MC, Cosmi F, et al. Insulin treatment and clinical outcomes in patients with diabetes and heart failure with preserved ejection fraction. Eur J Heart Fail. 2019;21:974-84. https://doi.org/10.1002/ejhf.1535

109. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393:31-9. https://doi.org/10.1016/S0140-6736(18)32590-X

110. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al.; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347-57. https://doi.org/10.1056/NEJMoa1812389

111. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation. 2019;139:2528-36. https://doi.org/10.1161/CIRCULATIONAHA.119.040130

112. McMurray JJV, DeMets DL, Inzucchi SE, Kober L, Kosiborod MN, Langkilde AM, et al.; on behalf of the DAPA-HF Committees and Investigators. The Dapagliflozin And Prevention of Adverse-outcomes in Heart Failure (DAPA-HF) trial: baseline characteristics. Eur J Heart Fail. 2019;21:1402-11. https://doi.org/10.1002/ejhf.1548

113. Martinez FA, Serenelli M, Nicolau JC, Petrie MC, Chiang CE, Tereshchenko S, et al. Efficacy and safety of dapagliflozin in heart failure with reduced ejection fraction according to age: insights from DAPA-HF. Circulation. 2020 Jan 14;141(2):100-111. https://doi.org/10.1161/circulationaha.119.044133

114. Kosiborod MN, Jhund P, Docherty KF, Diez M, Petrie MC, Verma S, et al. Effects of dapagliflozin on symptoms, function and quality of life in patients with heart failure and reduced ejection fraction: results from the DAPA-HF trial. Circulation. 2020 Jan 14;141(2):90-99. https://doi.org/10.1161/circulationaha.119.044138

115. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, et al.; On behalf of the DEFINE-HF Investigators. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. Circulation. 2019;140:1463-76. https://doi.org/10.1161/CIRCULATIONAHA.119.042929

116. Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. JAMA Cardiol. 2017;2:1025-9. https://doi.org/10.1001/jamacardio.2017.2275

117. Mazer CD, Hare GMT, Connelly PW, Gilbert RE, Shehata N, Quan A, et al. Effect of empagliflozin on erythropoietin levels, iron stores and red blood cell morphology in patients with type 2 diabetes and coronary artery disease. Circulation. 2020 Feb 25;141(8):704-707. https://doi.org/10.1161/circulationaha.119.044235

118. Swedberg K, Young JB, Anand S, Cheng S, Desai AS, Diaz R, et al.; RED-HF Committees, RED-HF Investigators. Treatment of anemia with darbepoetin alfa in systolic heart failure. N Engl J Med. 2013;368:1210-9. https://doi.org/10.1056/NEJMoa1214865

119. Packer M. Do sodium-glucose co-transporter-2 inhibitors prevent heart failure with a preserved ejection fraction by counterbalancing the effects of leptin? A novel hypothesis. Diabetes Obes Metab. 2018;20:1361-6. https://doi.org/10.1111/dom.13229

120. Nielsen R, Møller N, Gormsen LC, Tolbod LP, Hansson NH, Sorensen J, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. Circulation. 2019;139:2129-41. https://doi.org/10.1161/CIRCULATIONAHA.118.036459 121. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, et al. For the EMPA-HEART CardioLink-6 Investigators. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART cardiolink-6 randomized clinical trial. Circulation. 2019;140:1693-702. https://doi.org/10.1161/CIRCULATIONAHA.119.042375

122. Packer M, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al.; on behalf of the EMPEROR-Reduced Trial Committees and Investigators. Evaluation of the effect of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality of patients with chronic heart failure and a reduced ejection fraction: rationale for and design of the EMPEROR-Reduced trial. Eur J Heart Fail. 2019;21:1270-8. https://doi.org/10.1002/ejhf.1536

123 Anker SD, Butler J, Filippatos GS, Jamal W, Salsali A, Schnee J, et al.; on behalf of the EMPEROR-Preserved Trial Committees and Investigators. Evaluation of the effects of sodium-glucose co-transporter 2 inhibition with empagliflozin on morbidity and mortality in patients with chronic heart failure and a preserved ejection fraction: rationale for and design of the EMPEROR-Preserved Trial. Eur J Heart Fail. 2019;21:1279–87. https://doi.org/10.1002/ejhf.1596

124. Maggioni AP, Lopez-Sendon J, Nielsen OW, Hallen J, Aalamian-Mattheis M, Wang Y, et al. Efficacy and safety of serelaxin when added to standard of care in patients with acute heart failure: results from a PROBE study, RELAX-AHF-EU. Eur J Heart Fail. 2019;21:322–33. https://doi.org/10.1002/ejhf.1368

125. Metra M, Teerlink JR, Cotter G, Davison BA, Felker GM, Filippatos G, et al. van MW, von LD, Wikstrom G, Yilmaz MB, Hagner N, Holbro T, Hua TA, Sabarwal SV, Severin T, Szecsody P, Gimpelewicz C; RELAX-AHF-2 Committees Investigators. Effects of serelaxin in patients with acute heart failure. N Engl J Med. 2019;381:716–26. https://doi.org/10.1056/NEJMoa1801291

126. Kozhuharov N, Goudev A, Flores D, Maeder MT, Walter J, Shrestha S, et al. GALACTIC Investigators. Effect of a strategy of comprehensive vasodilation vs usual care on mortality and heart failure rehospitalization among patients with acute heart failure: The GALACTIC Randomized Clinical Trial. JAMA. 2019;322:2292–302. https://doi.org/10.1001/jama.2019.18598

127. Mebazaa A, Pang PS, Tavares M, Collins SP, Storrow AB, Laribi S, et al. The impact of early standard therapy on dyspnoea in patients with acute heart failure: the URGENT-dyspnoea study. Eur Heart J. 2010;31:832–41. https://doi.org/10.1093/eurheartj/ehp458

128. Biegus J, Zymlinski R, Siwolowski P, Testani J, Szachniewicz J, Tycińska A, et al. Controlled decongestion by reprieve therapy in acute heart failure: results of the TARGET-1 and TARGET-2 studies. Eur J Heart Fail. 2019;21:1079–87. https://doi.org/10.1002/ejhf.1533

129. Keeble TR, Karamasis GV, Rothman MT, Ricksten SE, Ferrari M, Hullin R, et al. Percutaneous haemodynamic and renal support in patients presenting with decompensated heart failure: a multi-centre efficacy study using the Reitan Catheter Pump (RCP). Int J Cardiol. 2019;275:53–8. https://doi.org/10.1016/j.ijcard.2018.09.085

130. Yau TM, Pagani FD, Mancini DM, Chang HL, Lala A, Woo YJ, et al.; for the Cardiothoracic Surgical Trials Network. Intramyocardial injection of mesenchymal precursor cells and successful temporary weaning from left ventricular assist device support in patients with advanced heart failure: a randomized clinical trial. JAMA. 2019;321:1176–86. https://doi.org/10.1001/jama.2019.2341

131. Garcia-Pavia P, Kim Y, Restrepo-Cordoba MA, Lunde IG, Wakimoto H, Smith AM, et al. Genetic variants associated with cancer therapy-induced cardiomyopathy. Circulation. 2019;140:31–41. https://doi.org/10.1161/CIRCULATIONAHA.118.037934

132. Yu AF, Yadav NU, Lung BY, Eaton AA, Thaler HT, Hudis CA, et al. Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer. Breast Cancer Res Treat. 2015;149:489–95. https://doi.org/10.1007/s10549-014-3253-7

133. Lynce F, Barac A, Geng X, Dang C, Yu AF, Smith KL, et al. Prospective evaluation of the cardiac safety of HER2-targeted therapies in patients with HER2-positive breast cancer and compromised heart function: the SAFE-HEaRt study. Breast Cancer Res Treat. 2019;175:595–603. https://doi.org/10.1007/s10549-019-05191-2

134. Cornell RF, Ky B, Weiss BM, Dahm CN, Gupta DK, Du L, et al. Prospective study of cardiac events during proteasome inhibitor therapy for relapsed multiple myeloma. J Clin Oncol. 2019;37:1946–55. https://doi.org/10.1200/JCO.19.00231

135. Abuosa AM, Elshiekh AH, Qureshi K, Abrar MB, Kholeif MA, Kinsara AJ, et al. Prophylactic use of carvedilol to prevent ventricular dysfunction in patients with cancer treated with doxorubicin. Indian Heart J. 2018;70 Suppl. 3:S96–100. https://doi.org/10.1016/j.ihj.2018.06.011

136. Li X, Li Y, Zhang T, Xiong X, Liu N, Pang B, et al. Role of cardioprotective agents on chemotherapy-induced heart failure: a systematic review and network meta-analysis of randomized controlled trials. Pharmacol Res. 2020;151:104577. https://doi.org/10.1016/j.phrs.2019.104577

137. Kapelios CJ, Lainscak M, Savarese G, Laroche C, Seferovic P, Ruschitzka F, et al. Sacubitril/valsartan eligibility and outcomes in the ESC-EORP-HFA Heart Failure Long-Term Registry: bridging between European Medicines Agency/Food and Drug Administration label, the PARADIGM-HF trial, ESC guidelines, and real world. Eur J Heart Fail. 2019;21:1383–97. https://doi.org/10.1002/ejhf.1532

138. Loop MS, van Dyke MK, Chen L, Safford MM, Kilgore ML, Brown TM, et al. Low utilization of beta-blockers among medicare beneficiaries hospitalized for heart failure with reduced ejection fraction. J Card Fail. 2019;25:343–51. https://doi.org/10.1016/j.cardfail.2018.10.005

139. Van Spall HGC, Lee SF, Xie F, Oz UE, Perez R, Mitoff PR, et al. Effect of patient-centered transitional care services on clinical outcomes in patients hospitalized for heart failure: the PACT-HF randomized clinical trial. JAMA. 2019;321:753–61. https://doi.org/10.1001/jama.2019.0710

140. Schulz M, Griese-Mammen N, Anker SD, Koehler F, Ihle P, Ruckes C, et al.; for the PHARM-CHF Investigators. Pharmacy-based interdisciplinary intervention for patients with chronic heart failure: results of the PHARM-CHF randomized controlled trial. Eur J Heart Fail. 2019;21:1012–21. https://doi.org/10.1002/ejhf.1503

141. Wagenaar KP, Broekhuizen BDL, Jaarsma T, Kok I, Mosterd A, Willems FF, et al. Effectiveness of the European Society of Cardiology/Heart Failure Association website 'heartfailurematters.org' and an e-health adjusted care pathway in patients with stable heart failure: results of the 'e-Vita HF' randomized controlled trial. Eur J Heart Fail. 2019;21:238–46. https://doi.org/10.1002/ejhf.1354

142. Shanbhag D, Graham ID, Harlos K, Haynes RB, Gabizon I, Connolly SJ, et al. Effectiveness of implementation interventions in improving physician adherence to guideline recommendations in heart failure: a systematic review. BMJ Open. 2018;8:e017765. https://doi.org/10.1136/bmjopen-2017-017765

143. Taylor RS, Long L, Mordi IR, Madsen MT, Davies EJ, Dalal H, et al. Exercise-based rehabilitation for heart failure: cochrane systematic review, meta-analysis, and trial sequential analysis. JACC Heart Fail. 2019;7:691–705. https://doi.org/10.1016/j.jchf.2019.04.023

144. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, et al. Impact of exercise rehabilitation on exercise capacity and quality-of-life in heart failure: individual participant meta-analysis. J Am Coll Cardiol. 2019;73:1430–43. https://doi.org/10.1016/j.jacc.2018.12.072

145. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, et al. on behalf of the ExTraMATCH II Collaboration. Impact of exercise-based cardiac rehabilitation in patients with heart failure (ExTraMATCH II) on mortality and hospitalisation: an individual patient data meta-analysis of randomised trials. Eur J Heart Fail. 2018;20:1735–43. https://doi.org/10.1002/ejhf.1311

146. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, et al. Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database Syst Rev. 2019;1:CD003331. https://doi.org/10.1002/14651858.CD003331.pub5

147. Takeda A, Martin N, Taylor RS, Taylor SJ. Disease management interventions for heart failure. Cochrane Database Syst Rev. 2019;1:CD002752. https://doi.org/10.1002/14651858.cd002752.pub4

148. Taylor RS, Sadler S, Dalal HM, Warren FC, Jolly K, Davis RC, et al. The cost effectiveness of REACH-HF and home-based cardiac rehabilitation compared with the usual medical care for heart failure with reduced ejection fraction: a decision model-based analysis. Eur J Prev Cardiol. 2019;26:1252–61. https://doi.org/10.1177/2047487319833507

149. Wingham J, Frost J, Britten N, Greaves C, Abraham C, Warren FC, et al. Caregiver outcomes of the REACH-HF multicentre randomized controlled trial of home-based rehabilitation for heart failure with reduced ejection fraction. Eur J Cardiovasc Nurs. 2019;18:611–20. https://doi.org/10.1177/1474515119850011

150. Johnson MJ, Cockayne S, Currow DC, Bell K, Hicks K, Fairhurst C, et al. Oral modified release morphine for breathlessness in chronic heart failure: a randomized placebo-controlled trial. ESC Heart Fail. 2019 Dec;6(6):1149-1160. https://doi.org/10.1002/ehf2.12498

151. Halliday BP, Wassall R, Lota AS, Khalique Z, Gregson J, Newsome S, et al. Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial. Lancet. 2019;393:61–73. https://doi.org/10.1016/S0140-6736(18)32484-X

152. Ghimire A, Fine N, Ezekowitz JA, Howlett J, Youngson E, McAlister FA. Frequency, predictors, and prognosis of ejection fraction improvement in heart failure: an echocardiogram-based registry study. Eur Heart J. 2019;40:2110-7. https://doi.org/10.1093/eurheartj/ehz233

153. Aguirre Dávila L, Weber K, Bavendiek U, Bauersachs J, Wittes J, Yusuf S, et al. Digoxin-mortality: randomized vs. observational comparison in the DIG trial. Eur Heart J. 2019;40:3336-41. https://doi.org/10.1093/eurheartj/ehz395

154. Rohde LE, Rover MM, Figueiredo Neto JA, Danzmann LC, Bertoldi EG, Simoes MV, et al. Raupp da RP, Biolo A. Short-term diuretic withdrawal in stable outpatients with mild heart failure and no fluid retention receiving optimal therapy: a double-blind, multicentre, randomized trial. Eur Heart J. 2019;40:3605-12. https://doi.org/10.1093/eurheartj/ehz554

155. Dovancescu S, Pellicori P, Mabote T, Torabi A, Clark AL, Cleland J. The effects of short-term omission of daily medication on the pathophysiology of heart failure. Eur J Heart Fail. 2017;19:643-9. https://doi.org/10.1002/ejhf.748