Novosti u dijagnostici i liječenju zatajivanja srca tijekom 2019. godine

Developments in Diagnosis and Treatment of Heart Failure in 2019

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Zatajivanje srca (ZS) jedan je od vodećih problema današnje. Klinički sindrom koji je na kraju kardiovaskularnog kontinua važan je ne samo kao značajan uzrok morbiditeta, mortaliteta i velikih ekonomskih troškova, nego i kao izazov za optimalnu primjenu dijagnostičkih metoda, algoritama za klasifikaciju i primjenu dokazano djelotvornih lijekova (poglašavaju skupine neurohormonalnih antagonista) ili elektroničkih ugradbenih srčanih uređaja.1,2

U posljednjim desetljećima niz izstupavanja i aktivnosti kojima su predmet interesa optimalno zbrinjavanje bolesnika, poboljšanje kvalitete života i podizanje svijesti o ZS-u, koje se provode diljem svijeta. Članovi Hrvatskoga kardiološkog društva također kontinuirano podižu svijest o ZS-u, dakle vrlo važno ne samo kao značajno uzroka zdravstvenih stavki, vjerojatno malog pretpovršina, simptom ZS-a, postavljanja točne dijagnoze i optimalnog liječenja.2 Osim Hrvatskog registra zatajivanja srca2,3 znanstvenih i stručnih članaka i skupova, u svibnju 2020. godine obilježavaju su i Dni svjetlosti o zatajivanju srca4.

O uvome broju časopis Cardiologia Croatica stoga smo kao vodeću temu izabrali novosti v području ZS-a, ovaj put u suradnji s dvama stručnim udruženjima. U tekstu koji je sastavni dio ovoga specijalnog članka donosimo prijevod sažetaka triju metaanaliza koje je nedavno objavila skupina Cochrane Heart, koja ova saznanja želi protjeriti i među članovima Hrvatskoga kardiološkog društva.2,3

Heart failure (HF) is currently one of the leading healthcare problems in the world. This clinical syndrome is at the end of the cardiovascular continuum and is important not only as a significant cause of morbidity, mortality, and large economic burden, but also represents a challenge in the optimal application of diagnostic methods, risk stratification, and evidence-based application of effective medication (especially from the neurohormonal antagonist group) or electronic implantable heart devices.1,2

Over the last decades, a number of studies and activities have been conducted all around the world with the goal of achieving optimal patient care, improving quality of live, and improving awareness of HF. The members of the Croatian Cardiac Society also continuously work to raise awareness on the importance of early recognition of HF symptoms, establishing the correct diagnosis, and implementing optimal treatment. In addition to the Croatian Heart Failure Registry3 and scientific and professional articles and meetings, the Heart Failure Awareness Day is to be held in May 2020.4

We have therefore selected developments related to HF as the leading topic of this issue of the Cardiologia Croatica journal, this time in cooperation with two professional societies. The main body of this article features a translation of the summaries of three meta-analyses recently published by the
liječenje vodeno natriuretskim peptidima u prevenciji kardiovaskularnih događaja u pacijenata bez zatajivanja srca: Cochrane sustavni pregled

Natriuretski peptidi (NPs), uključujući B-tip natriuretskog peptida (BNP) i N-terminal pro B-tip natriuretskog peptida (NT-proBNP) dobro su poznati bilježi za otkrivanje i dijagnosticiranje zdravlja i perifernih arterija. Sve navedene članke preveli su članovi Uredničkog odbora časopisa Cardiologia Croatica.

Cilj
Cilj ovog ispitivanja bio je proučiti učinak liječenja koristeći natriuretskim peptidima (NP) u osoba s KV čimbenicima rizika, bez znakova ZS-a

Metode ispitivanja
Pretraživale su se sljedeće bibliografske baze podataka, do 9. srpnja 2019. CENTRAL, MEDLINE, EMBASE, Web of Science. Tri registra kliničkih ispitivanja također su se istraživala u srpnju 2019.

Kriteriji odabira
U ispitivanje su uključena randomizirana kontrolirana ispitivanja odraslih osoba s jednim ili više KV čimbenika rizika, bez znakova ZS-a, koje su uspoređivale probir i vodeno liječenje natriuretskim peptidima.

Natriuretic peptide-guided treatment for the prevention of cardiovascular events in patients without heart failure: a Cochrane systematic review

Natriuretic peptides (NPs), including B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP), are well-established biomarkers for the detection and diagnostic evaluation of heart failure. They are of interest for CVD prevention because they are secreted by the heart as a protective response to cardiovascular stress, strain, and damage. Therefore, measuring NP levels in patients without heart failure may be valuable for risk stratification, to identify those at highest risk of CVD who would benefit most from intensive risk reduction measures.

Objectives
To assess the effects of natriuretic peptide (NP)-guided treatment for people with cardiovascular risk factors and without heart failure.

Search methods
Searches of the following bibliographic databases were conducted up to 9 July 2019: CENTRAL, MEDLINE, Embase, and Web of Science. Three clinical trial registries were also searched in July 2019.

Selection criteria
We included randomized controlled trials enrolling adults with one or more cardiovascular risk factors and without heart failure, which compared NP-based screening and sub-
 čenje na temelju vrijednosti NP-a s obzirom na standardni pristup u odgovarajućim okolnostima (npr. u bolnici, u populaciji).

**Prikupljanje podataka i analiza**

Autori ispitivanja neovisno su pretraživali naslove i sažetke, odabrali ispitivanja koje će se uključiti, preuzimali i sažimali podatke i procijenili rizik. Omjeri rizika (eng. *risk ratio*, RR) računani su za dihotomne podatke, a srednja razlika (eng. *mean difference*, MDs) s 95 %-tnim intervalom pouzdanosti – (CI) rabilo se za kontinuirane podatke. Dodatno su kontaktirani autori nekih ispitivanja poradim procjene ključnih studijskih obilježja. Uporabljajući GRADE pristup (Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, two review authors independently assessed the quality of the evidence and GRADE profiler (GRADEPRO) was used to import data from Review Manager to create a 'Summary of findings' table.

**Glavni rezultati**

U ispitivanje su uključene dva randomizirana kontrolirana ispitivanja (3 izvještaja) s ukupno 1674 ispitanika, srednje dobi između 64,1 i 67,8 godina. Praćenje je prosječno trajalo od 2 do 4,3 godine.

Što se tiče primarnog cilja ispitivanja, rezultat se procijenio iz jednog ispitivanja i nije se dokazao siguran učinak terapije vođene pomoću NP-a na KV mortalitet u bolesnika s KV čimbenicima rizika i bez znakova ZS-a (RR 0,33, 95 % CI 0,04 do 3,17; 1 ispitivanje; 300 ispitanika; dokaz niske kvalitete). Sveobuhvatna analiza pokazuje da, u usporedbi sa standardnim postupcima, vođeno liječenje s pomoću NP-a vjerojatno smanjuje rizik od CV hospitalizacije (RR 0,52, 95 % CI 0,40 do 0,68; 2 ispitivanja, 1674 ispitanika; dokaz srednje kvalitete). Ovo korelira s rizikom od 163 na 1000 u kontrolnoj skupini i 85 (95 % CI 65 do 111) na 1000 u grupi uz vođenu terapiju s pomoću NP-a.

Analizirajući sekundarni cilj ispitivanja, podatci pokazuju da nije siguran učinak vođenog liječenja s pomoću NP-a s obzirom na sve uzroke smrti (RR 0,90, 95 % CI 0,60 do 1,35; 2 ispitivanja, 1354 ispitanika; dokaz niske kvalitete). Ukupna analiza rezultata upućuje na to da vođeno liječenje s pomoću NP-a vjerojatno smanjuje rizik od svih vrsta hospitalizacije (RR 0,83, 95 % CI 0,75 do 0,92; 2 ispitivanja, 1354 ispitanika; dokaz srednje kvalitete). Ovo korespondira s rizikom od 601 na 1000 u kontrolnoj skupini i 499 (95 % CI 457 do 553) na 1000 u NP-om vođenoj terapijskoj skupini. Navedeni rezultat iz jednog ispitivanja pokazuje da vođeno liječenje s pomoću NP-a smanjuje rizik od disfunkcije klijetki (RR 0,61, 95 % CI 0,41 do 0,91; 1374 ispitanika; dokaz visoke kvalitete). Rizik u kontrolnoj skupini bio je 87 na 1000, u usporedbi s 53 (95 % CI 36 do 79) na 1000 u NP-om vođenoj terapijskoj skupini. Rezultati istog ispitivanja pokazuju da NP-om vođeno liječenje ne utječe na promjene u razini: NP-a na kraju vremena praćenja u usporedbi sa standardnim pristupom (MD – 4,06 pg/mL, 95 % CI 15,07 do 6,95; ispitivanje; 1374 ispitanika; dokaz srednje kvalitete).

**Zaključci**

Ovaj Cochraneov sustavni pregled pokazuje da liječenje vođeno pomoću NP-a pomaže u smanjenju hospitalizacije zbog KV i svih drugih razloga, kao i pojavnosti disfunkcije klijetki, za bolesnike s KV čimbenicima rizika, bez znakova ZS-a. Učinci na na smrtnost i vrijednosti NP-a, manje su sigurni. Njedno od uključenih ispitivanja nije imala dovoljnu snagu za procjenu smrtnosti. Raspolozivi podacima rezultat pokazuje da, što seuent NP-guided treatment versus standard care in all settings (i.e. community, hospital).

**Data collection and analysis**

Two review authors independently screened titles and abstracts and selected studies for inclusion, extracted data, and evaluated risk of bias. Risk ratios (RRs) were calculated for dichotomous data, and mean differences (MDs) with 95% confidence intervals (CIs) were calculated for continuous data. We contacted trial authors to obtain missing data and to verify crucial study characteristics. Using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, two review authors independently assessed the quality of the evidence and GRADE profiler (GRADEPRO) was used to import data from Review Manager to create a ‘Summary of findings’ table.

**Main results**

We included two randomized controlled trials (three reports) with 1674 participants, with mean age between 64.1 and 67.8 years. Follow-up ranged from 2 years to mean 4.3 years.

For primary outcome measures, effect estimates from a single study showed uncertainty for the effect of NP-guided treatment on cardiovascular mortality in patients with cardiovascular risk factors and without heart failure (RR 0.33, 95% CI 0.04 to 3.17; 1 study, 300 participants; low-quality evidence). Pooled analysis demonstrated that in comparison to standard care, NP-guided treatment probably reduces the risk of cardiovascular hospitalization (RR 0.52, 95% CI 0.40 to 0.68; 2 studies, 1674 participants; moderate-quality evidence). This corresponds to a risk of 163 per 1000 in the control group and 85 (95% CI 65 to 111) per 1000 in the NP-guided treatment group.

When secondary outcome measures were evaluated, evidence from a pooled analysis showed uncertainty for the effect of NP-guided treatment on all-cause mortality (RR 0.90, 95% CI 0.60 to 1.35; 2 studies, 1354 participants; low-quality evidence). Pooled analysis indicates that NP-guided treatment probably reduces the risk of all-cause hospitalization (RR 0.83, 95% CI 0.75 to 0.92; 2 studies, 1354 participants; moderate-quality evidence). This corresponds to a risk of 601 per 1000 in the control group and 499 (95% CI 457 to 553) per 1000 in the NP-guided treatment group. The effect estimate from a single study indicates that NP-guided treatment reduced the risk of ventricular dysfunction (RR 0.61, 95% CI 0.41 to 0.91; 1374 participants; high-quality evidence). The risk in this study’s control group was 87 per 1000, compared with 53 (95% CI 36 to 79) per 1000 with NP-guided treatment. Results from the same study show that NP-guided treatment does not affect change in NP level at the end of follow-up, relative to standard care (MD -4.06 pg/mL, 95% CI -15.07 to 6.95; 1 study, 1374 participants; moderate-quality evidence).

**Authors’ conclusions**

This review shows that NP-guided treatment is likely to reduce ventricular dysfunction and cardiovascular and all-cause hospitalization for patients who have cardiovascular risk factors and who do not have heart failure. Effects on mortality and natriuretic peptide levels are less certain. Neither of the included studies were powered to evaluate mortality. Available evidence shows uncertainty regarding the effects of NP-guided treatment on both cardiovascular mortality and all-cause mortality; very low event numbers resulted in a high
se tiže učinaka vođenog liječenja s pomoću NP-a na KV, kao i opći mortalitet, procjena nije sigurna. Vrlo malo broj ovakvih događaja u ispitivanjima rezultira visokim stupnjem nepreciznosti, a da bi se učinak mogao adekvatno procijeniti. Podatci također pokazuju da NP-om vođeno liječenje možda neće utjecati na vrijednosti NP-a pri kraju razdoblja praćenja.

Oba ispitivanja uključena u ovaj pregled bila su pragmatičnog dizajna, u stvarnim kliničkim okruženjima, i nisu bila dvostruko slijepa. Potrebna su daljnja ispitivanja, s primjerom veličinom uzorka i duljim vremenom praćenja kako bi se adekvatno procijenio učinak vođenog liječenja s pomoću NP-a na smrtnost. Dva su ispitivanja u tijeku, od kojih je jedno veliko, multicentrično. U budućnosti se očekuju ispitivanja s većim brojem ispitanika iz šireg zemljopisnog područja.

**Beta-blokatori i inhibitori reninsko-angio-tensinsko-aldosteronskog sustava u kroničnom zatajivanju srca s očuvanom sistoličkom funkcijom lijeve klijetke:**

Cochrane sustavni pregled

(Prijedvod znanstvenog sažetka Cochraneovog sustavnog pregleda literature objeđenog u: Martin N, Manoharan K, Thomas J, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database Syst Rev. 2018 Jun 28;6:CD012721. https://doi.org/10.1002/14651858.CD012721.pub2)

Beta-blokatori i inhibitori reninsko-angiotensinsko-aldosteronskog sustava poboljšavaju preživljavanje i smanjuju mrtvuljivost, posebno kod pacijenata s sistemom lijeve klijetke. Nije sigurno može li takvo liječenje pomoći i osobama sa nezdravim dizajnom, u stvarnim kliničkim okruženjima, i nisu bila dvostruko slijepa. Potrebna su daljnja ispitivanja, s primjerom veličinom uzorka i duljim vremenom praćenja kako bi se adekvatno procijenio učinak vođenog liječenja s pomoću NP-a na smrtnost. Dva su ispitivanja u tijeku, od kojih je jedno veliko, multicentrično. U budućnosti se očekuju ispitivanja s većim brojem ispitanika iz šireg zemljopisnog područja.

**Ciljevi**

Cilj je ispitivanja bio proučiti učinak beta-blokatora, inhibitora angiotenzin konvertirajućeg enzima, blokatora angiotenzinskih receptorima, angiotenzin receptor neprilizin inhibitora i antagonista mineralokortikoidnih receptorima, u bolesnika sa ZS-om i očuvanom sistoličkom funkcijom lijeve klijetke. Nije sigurno može li takvo liječenje pomoći i osobama sa ZS-om i očuvanom sistoličkom funkcijom lijeve klijetke (eng. *heart failure with preserved ejection fraction*, HFpEF), tako da je potrebno sveobuhvatnije proučiti ispitivanja iz ovog područja.

**Metode ispitivanja**

Analizirani su CENTRAL, MEDLINE i EMBASE baza podataka, kao i dva registra kliničkih ispitivanja 27. srpnja 2017. kako bi se pronašla prihvatljiva ispitivanja. Lista referencija iz primarnih ispitivanja i pregledni članci pretraženi su za dodatna ispitivanja za uključenje. Nije bilo jezičnih ili podatkovnih ograničenja.

**Kriteriji odabira**

Uključena su randomizirana kontrolirana ispitivanja paralelnog dizajna, koja su uključivala odrasle ispitanike sa ZS-om i očuvanom sistoličkom funkcijom lijeve klijetke, definiranom kao istinska frakcija veća od 40 %.

**Prikupljanje podataka i analiza**

Autori pregleda neovisno su odabrali ispitivanja za uključenje u analizu i preuzimanje podataka. Proučavani su ishodi uključenih KV mortalitet, hospitalizaciju zbog ZS-a, hiperkalemiju, all-cause mortalitet, procjena nije sigurna. Vrlo mali broj ovakvih događaja u ispitivanjima rezultira visokim stupnjem nepreciznosti, a da bi se učinak mogao adekvatno procijeniti. Podatci također pokazuju da NP-om vođeno liječenje možda neće utjecati na vrijednosti NP-a pri kraju razdoblja praćenja.

As both trials included in our review were pragmatic studies, non-blindning of patients and practices may have biased results towards a finding of equivalence. Further studies with more adequately powered sample sizes and longer duration of follow-up are required to evaluate the effect of NP-guided treatment on mortality. As two trials are ongoing, one of which is a large multicenter trial, it is hoped that future iterations of this review will benefit from larger sample sizes across a wider geographical area.

**Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction: a Cochrane systematic review**

(translation of the Cochrane systematic review abstract published in: Martin N, Manoharan K, Thomas J, Davies C, Lumbers RT. Beta-blockers and inhibitors of the renin-angiotensin aldosterone system for chronic heart failure with preserved ejection fraction. Cochrane Database Syst Rev. 2018 Jun 28;6:CD012721. https://doi.org/10.1002/14651858.CD012721.pub2)

Beta-blockers and inhibitors of the renin-angiotensin aldosterone system improve survival and reduce morbidity in people with heart failure with reduced left ventricular ejection fraction. There is uncertainty whether these treatments are beneficial for people with heart failure with preserved ejection fraction and a comprehensive review of the evidence is required.

**Objectives**

To assess the effects of beta-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilisin inhibitors, and mineralocorticoid receptor antagonists in people with heart failure with preserved ejection fraction.

**Search methods**

We searched CENTRAL, MEDLINE, Embase and two clinical trial registries on 25 July 2017 to identify eligible studies. Reference lists from primary studies and review articles were checked for additional studies. There were no language or date restrictions.

**Selection criteria**

We included randomized controlled trials with a parallel group design enrolling adult participants with heart failure with preserved ejection fraction, defined by a left ventricular ejection fraction of greater than 40 percent.

**Data collection and analysis**

Two review authors independently selected studies for inclusion and extracted data. The outcomes assessed included cardiovascular mortality, heart failure hospitalization, hyperkalemia, all-cause mortality and quality of life. Risk ratios (RR) and, where possible, hazard ratios (HR) were calculated for dichotomous outcomes. For continuous data, mean difference (MD) or standardized mean difference (SMD) were...
Glavni rezultati

Trideset sedam randomiziranih kontroliranih ispitivanja s ukupno 18 311 ispitanika.

Uključeno je deset ispitivanja (3087 ispitanika) koje su pro- učavale beta-blokatore (BB). Sveukupna analiza podataka upućuje na smanjenje KV mortaliteta (15 % ispitanika u interven- cijalnoj skupini prema 19 % u kontrolnoj skupini, RR 0,78; 95 %-ni interval pouzdanosti – CI 0,62 do 0,99; NNTB 25; 1046 ispitanika; 3 ispitivanja). No, riječ je bila dokazama niske kvalitete i nije se pokazalo povoljan učinak na KV mortali- let, kada je analiza bila ograničena na ispitivanja s niskim ri- zikom od pristranosti (RR 0,81; 95% CI 0,50 do 1,29; 643 ispitanika; 1 ispitivanje). Nije bilo učinaka ni na sve vrste mortaliteta, hospitalizaciju zbog ZS-a ili kvalitetu života, no zaključci nisu potpuno pouzdani s obzirom na ograničenost razine dokaza.

Nadalje, uključeno je 12 ispitivanja (4408 ispitanika) koje su pro- učavale antagoniste mineralokortikoidnih receptora (MRA) sa srednjom kvalitetom dokaza. Liječenje primjenom MRA-a smanjuje broj hospitalizacija zbog ZS-a (11 % ispitanika u intervencijskoj skupini prema 14 % u kontrolnoj skupini; RR 0,82; 95% CI 0,69 do 0,98; NNTB 41; 3714 ispitanika; 3 ispitiva- nja, srednja kvaliteta dokaza), no pokazao se mali ili nikakav učinak u intervencijskoj skupini prema 0,5 % u kontrolnoj skupini; RR 1,88, 95% CI 1,07 do 3,33; 7148 ispitanika, 2 ispitiva- nj. Nije bilo učinaka ni na sve vrste mortaliteta, hospitalizaciju zbog ZS-a ili kvalitetu života, no zaključci nisu potpuno pouzdani s obzirom na ograničenost razine dokaza.

Analizirano je 8 ispitivanja (2061 ispitanika) koje su pro- učavale inhibitore angiotenzin konvertirajućeg enzima (ACEI), sa srednjom kvalitetom dokaza. Podatci su pokazali da liječenje primjenom ACEI ima mali ili nikakav učinak na KV mortalit- let, opći mortalitet, hospitalizaciju zbog ZS ili kvalitetu živo- ta. Podatci o učinku ACEI-ja na hiperkalemiju navedeni su u samo jednom od ispitivanja.

Uključeno je osam ispitivanja (8755 ispitanika) koje su pro- učavale angiotenzin receptor blokatore (ARB), sa visokom kvalitetom dokaza. Podatci pokazuju da liječenje primjenom ARB ima mali ili nikakav učinak na KV mortalitet, opći mortalitet, hospitalizaciju zbog ZS ili kvalitetu života. Primjena ARB je povezana s povećanim rizikom od hiperkalemije (0,9 % ispitanika u intervencijskoj skupini prema 0,5 % u kontrolnoj skupini; RR 1,88, 95 % CI 1,07 do 3,33; 7148 ispitanika, 2 ispitivanja, visoka kvaliteta dokaza).

Jedno placebom kontrolirano ispitivanje, koje je juž u tije- ku i nema objavljenih rezultata, proučava učinak angiotenzin receptor neprilizin inhibitora (ARNI) u bolesnika sa ZS-om i očuvanom sistoličkom funkcijom lijeve klijetke.

Zaključci

Analizirani podatci pokazuju da liječenje primjenom MRA-a smanjuje broj hospitalizacija zbog ZS-a u osoba sa ZS-om i očuvanom sistoličkom funkcijom lijeve klijetke, no učinak na mortalitet i kvalitetu života ostaje nejasan. Raspolaživi podatci o liječenju primjenom lijekova iz skupine BB, ACEI, ARB i ARNI calculated. We contacted trialists where necessary to obtain missing data.

Main results

37 randomized controlled trials (207 reports) were included across all comparisons with a total of 18,311 participants.

Ten studies (3087 participants) investigating beta-blockers (BB) were included. A pooled analysis indicated a reduction in cardiovascular mortality (15% of participants in the interven- tion arm versus 19% in the control arm; RR 0.78; 95% confidence interval (CI) 0.62 to 0.99; number needed to treat to benefit (NNTB) 25; 1046 participants; 3 studies). However, the quality of evidence was low and no effect on cardiovascular mortality was observed when the analysis was limited to studies with a low risk of bias (RR 0.81; 95% CI 0.50 to 1.29; 643 participants; 1 study). There was no effect on all-cause mor- tality, heart failure hospitalization or quality of life measures, however there is uncertainty about these effects given the limited evidence available.

12 studies (4408 participants) investigating mineralocorti- coid receptor antagonists (MRA) were included with the quality of evidence assessed as moderate. MRA treatment reduced heart failure hospitalization (11% of participants in the inter- vention arm versus 14% in the control arm; RR 0.82; 95% CI 0.69 to 0.98; NNTB 41; 3714 participants; 3 studies; moderate- quality evidence) however, little or no effect on all-cause and cardiovascular mortality and quality of life measures was observed. MRA treatment was associated with a greater risk of hyperkalemia (16% of participants in the intervention group versus 8% in the control group; RR 2.11; 95% CI 1.77 to 2.51; 4291 participants; 6 studies; high-quality evidence).

Eight studies (2061 participants) investigating angioten- sin converting enzyme inhibitors (ACEI) were included with the overall quality of evidence assessed as moderate. The evidence suggested that ACEI treatment likely has little or no effect on cardiovascular mortality, all-cause mortality, heart failure hospitalization, or quality of life. Data for the effect of ACEI on hyperkalemia were only available from one of the included studies.

Eight studies (8755 participants) investigating angiotensin receptor blockers (ARB) were included with the overall quality of evidence assessed as high. The evidence suggested that treatment with ARB has little or no effect on cardiovascular mortality, all-cause mortality, heart failure hospitalization, or quality of life. ARB was associated with an increased risk of hyperkalemia (0.9% of participants in the intervention group versus 0.5% in the control group; RR 1.88; 95% CI 1.07 to 3.33; 7148 participants; 2 studies; high-quality evidence).

We identified a single ongoing placebo-controlled study investigating the effect of angiotensin receptor neprilisin inhibitors (ARNI) in people with heart failure with preserved ejection fraction.

Authors’ conclusions

There is evidence that MRA treatment reduces heart failure hospitalization in heart failure with preserved ejection frac- tion, however the effects on mortality related outcomes and quality of life remain unclear. The available evidence for beta- blockers, ACEI, ARB and ARNI is limited and it remains un- certain whether these treatments have a role in the treatment of HFpEF in the absence of an alternative indication for their
ogranicieni su i nije sigurno imaju li ulogu u bolesnika s HFpEF-om, a u odzivotnosti alternativne indicacije za njihovu uporabu. Ovo opsežno ispitivanje naglašava postojeću nedostatnost podataka s obzirom na sadašnje znanje i bit će potrebno pričekati rezultate velikih kliničkih ispitivanja od kojih su neka u tijeku.

Liječenje zatajivanja srca dodatnim interventijskim metodama: Cochrane sustavni pregled

(prijedv znanstvenog sažetka Cochraneovog sustavnog pregleda liternutur u objavljenog u: Takeda A, Martin N, Taylor RS, Taylor SJ. Disease management interventions for heart failure. Cochrane Database Syst Rev. 2019 Jan 8;1:CD002752. https://doi.org/10.1002/14651858.CD002752.pub4)

Unatoč napretku u liječenju, populacija bolnih, bolesnika od ZS-a sve je veća, što ide i uz starenje svjetske populacije. Zahajanje srca i nije uputno osloniti se samo na medikamentno liječenje. Ovo opsežno ispitivanje naglašava postojeću nedostatnost podataka s obzirom na sadašnje znanje i bit će potrebno pričekati rezultate velikih kliničkih ispitivanja od kojih su neka u tijeku.

Disease management interventions for heart failure: a Cochrane systematic review

(translation of the Cochrane systematic review abstract published in: Take-da A, Martin N, Taylor RS, Taylor SJ. Disease management interventions for heart failure. Cochrane Database Syst Rev. 2019 Jan 8;1:CD002752. https://doi.org/10.1002/14651858.CD002752.pub4)

Despite advances in treatment, the increasing and ageing population makes heart failure an important cause of morbidity and death worldwide. It is associated with high healthcare costs, partly driven by frequent hospital readmissions. Disease management interventions may help to manage people with heart failure in a more proactive, preventative way than drug therapy alone. This is the second update of a review published in 2005 and updated in 2012.

Objectives

To compare the effects of different disease management interventions for heart failure (which are not purely educational in focus), with usual care, in terms of death, hospital readmissions, quality of life and cost-related outcomes.

Selection criteria

We included randomized controlled trials (RCTs) with at least six months' follow-up, comparing disease management interventions to usual care for adults who had been admitted to hospital at least once with a diagnosis of heart failure. There were three main types of intervention: case management; clinic-based interventions; multidisciplinary interventions.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Outcomes of interest were mortality due to heart failure, mortality due to any cause, hospital readmission for heart failure, hospital readmission for any cause, adverse effects, quality of life, costs and cost-effectiveness.

Main results

We found 22 new RCTs, so now include 47 RCTs (10,869 participants). Twenty-eight were case management interventions, seven were clinic-based models, nine were multidisciplinary interventions, and three could not be categorized as any of these. The included studies were predominantly in an older population, with most studies reporting a mean age of between 67 and 80 years. Seven RCTs were in upper-middle-income countries, the rest were in high-income countries.

Only two multidisciplinary-intervention RCTs reported mortality due to heart failure. Pooled analysis gave a risk ratio (RR) of 0.46 (95% confidence interval (CI) 0.23 to 0.95), but the very low-quality evidence means we are uncertain of the
koristilo se individualnim intervencijama, sedam interven-
cijama temeljenima na kliničkom praćenju, devet multidisci-
plinarim intervencijama, a tri svima navedenima. Uključe-
na ispitivanja su uglavnom obuhvaćale stariju populaciju, a
većina ispitanika bila je prosječne dobi između 67 i 80 godina.
Sedam RCT-a bilo je iz ekonomski visoko-srednje razvijenih
zemlja, a ostatak iz ekonomski srednjih zemalja.

Samuva multidisciplinarna intervencija RCT-a izvijesti-
la su o mortalitetu zbog ZS-a. Skupna analiza pokazuje omjer
rizika (RR) od 0,46 (95 %-ni interval pouzdanosti – CI 0,23 do
0,95), no riječ je o vrlo niskoj kvaliteti dokaza, što znači da nismo
sigurni kakav je učinak na mortalitet vezan uz ZS. Temeljeno
na ovim ograničenim podacima NNTB je 12 (95 % CI 9 do 126).
Dvadeset šest RCT-a koji su se koristili individualnom interven-
cijom izvješćivalo je o svim uzorcima smrti, uz dokaze niske
kvalitete, rezultati govore u prilog sniznju ukupne smrtnosti
(RR 0,78, 95 % CI 0,66 do 0,90; NNTB 25, 95 % CI 17 do 54). Skupni
podatci sedam RCT-a s intervencijama temeljenima na klinič-
kom praćenju, uz dokaze niske kvalitete, opisuju malu ili nika-
kvu razliku s obzirom na sve vrste mortaliteta. Skupna analiza
osam multidisciplinarnih ispitivanja, uz srednju kvalitetu do-
kaza, pokazuje da vjerojatno postoji smanjenje svih vrsta mor-
taliteta (RR 0,67, 95 % CI 0,54 do 0,83; NNTB 17, 95 % CI 12 do 32).

Analizirani su skupni podatci o ponavljanim hospitalizaci-
jama zbog ZS-a iz 12 ispitivanja koje su se koristile individu-
alnim intervencijama. Uz srednju kvalitetu dokaza, rezultati
pokazuju da je vjerojatno riječ o malom ili nikakvom učinku na ponavljane
hospitalizacije zbog ZS-a, u usporedbi sa standardnim zbrin-
javanjem bolesnika (RR 1,01, 95 % CI 0,87 do 118). Skupna ana-
liza 5 RCT-a s multidisciplinarnim intervencijama uz nisku
kvalitetu dokaza pokazuje smanjenje rizika od ponavljanih
hospitalizacija zbog ZS-a (RR 0,68, 95 % CI 0,50 do 0,92; NNTB
11, 95 % CI 7 do 44). Metaanaliza 14 RCT-a, uz srednju kvali-
tetu dokaza, pokazuje da individualne intervencije vjerojatno
blago smanjuju broj svih vrsta ponavljanih hospitalizacija (RR
0,92, 95 % CI 0,83 do 1,02; sniznje s 491 na 451 u 1000 ispitani-
ika (95 % CI 407 do 495). Skupni podatci 4 RCT-a s intervenci-
jamama temeljenima na kliničkom praćenju, uz nisku kvalitetu
heterogenih dokaza, pokazuju malu ili nikakvu razliku svih
uzroka ponavljanih hospitalizacija (RR 0,90, 95 % CI 0,72 do
1,12). Pet RCT-a, uz nisku kvalitetu dokaza, pokazuje da mul-
disciplinarne intervencije mogu blago smanjiti ponavljane
hospitalizacije zbog svih uzroka (RR 0,85, 95 % CI 0,71 do 1,01);
sniznje od 450 s 383 na 1000 ispitanika (95 % CI 320 do 455).

Njedno ispitivanje individualne intervencije, kao ni inter-
vencije temeljene na kliničkom praćenju, nije izvještavalo o
neželjenim učincima. Dva multidisciplinarna intervencijaka
ispitivanja govore o tome da nije bilo neželjenih učinaka.
GRADE procjena srednje kvalitete govori da moguće ima male
ili nikakve razlike u neželjenim učincima između multidisci-
plinarnih intervencija i standarnog zbrinjavanja.

O kvaliteti života općenito se malo izvještava. Nije sigurno
da individualne intervencije, kao i multidisciplinarne inter-
vencije utječu na kvalitetu života, uz dokaze niske kvalitete.
Četiri ispitivanja koristila su se intervencijama temeljenima
na kliničkom praćenju, no rezultati se nisu mogli analizirati
zbog razlika u izvještavanju. Dokazi niske kvalitete govore u
prilog tomu da ova vrsta intervencije rezultira malim ili nika-
kvim razlikama u kvaliteti života.

Effect on mortality due to heart failure. Based on this limited
evidence, the number needed to treat for an additional benefi-
cial outcome (NNTB) is 12 (95 % CI 9 to 126).

Twenty-six case management RCTs reported all-cause
mortality, with low-quality evidence indicating that these
can reduce all-cause mortality (RR 0.78, 95 % CI 0.66 to 0.90;
NNTB 25, 95 % CI 17 to 54). We pooled all seven clinic-based
studies, with low-quality evidence suggesting they may make
little or no difference to all-cause mortality. Pooled analysis
of eight multidisciplinary studies gave moderate-quality evi-
dence that these probably reduce all-cause mortality (RR 0.67,
95 % CI 0.54 to 0.83; NNTB 17, 95 % CI 12 to 32).

We pooled data on heart failure readmissions from 12 case
management studies. Moderate-quality evidence suggests that
they probably reduce heart failure readmissions (RR 0.64,
95 % CI 0.53 to 0.79; NNTB 8, 95 % CI 6 to 13). We were able to
pool only two clinic-based studies, and the moderate-quality evi-
dence suggested that there is probably little or no difference in
heart failure readmissions between clinic-based interventions
and usual care (RR 1.01, 95 % CI 0.87 to 118). Pooled anal-
ysis of five multidisciplinary interventions gave low-quality
evidence that these may reduce the risk of heart failure read-
missions (RR 0.68, 95 % CI 0.50 to 0.92; NNTB 11, 95 % CI 7 to 44).

Meta-analysis of 14 RCTs gave moderate-quality evidence
that case management probably slightly reduces all-cause re-
admissions (RR 0.92, 95 % CI 0.83 to 1.01), a decrease from 491
to 451 in 1000 people (95 % CI 407 to 495). Pooled four clinic-
based RCTs gave low-quality and somewhat heterogeneous
evidence that these may result in little or no difference in all-
cause readmissions (RR 0.90, 95 % CI 0.72 to 112). Low-quality
evidence from five RCTs indicated that multidisciplinary in-
terventions may slightly reduce all-cause readmissions (RR
0.85, 95 % CI 0.71 to 1.01); a decrease from 450 to 383 in 1000
people (95 % CI 320 to 455).

Neither case management nor clinic-based intervention
RCTs reported adverse effects. Two multidisciplinary inter-
ventions reported that no adverse events occurred. GRADE
assessment of moderate quality suggested that there may be
little or no difference in adverse effects between multidisci-
plinary interventions and usual care.

Quality of life was generally poorly reported, with high at-
trition. Low-quality evidence means we are uncertain about
the effect of case management and multidisciplinary inter-
ventions on quality of life. Four clinic-based studies reported
quality of life but we could not pool them due to differences in
reporting. Low-quality evidence indicates that clinic-based
interventions may result in little or no difference in quality of
life.

Four case management programmes had cost-effective-
ness analyses, and seven reported cost data. Low-quality
evidence indicates that these may reduce costs and may be
cost-effective. Two clinic-based studies reported cost sav-
ings. Low-quality evidence indicates that clinic-based inter-
ventions may reduce costs slightly. Low-quality data from
one multidisciplinary intervention suggested this may be
cost-effective from a societal perspective but less so from a
health-services perspective.

Authors’ conclusions
We found limited evidence for the effect of disease manage-
ment programmes on mortality due to heart failure, with few
Četiri RCT-a koja su koristila individualne intervencije napravila su analizu troškovne učinkovitosti, a sedam je iz spektive zdravstvenog sustava.

Zaključci
Nađeni su ograničeni dokazi o učincima intervencijalnih programa na mortalitet zbog ZS-a na temelju nekoliko ispitivanja koje su izvještavale o tom ishodu. Individualne intervencije mogu smanjiti sve vrste mortaliteta. Multidisciplinarne intervencije vjerovatno, isto tako, reduciraju sve vrste mortaliteta, dok intervencije temeljene na kliničkom pručenju imaju mali ili nikakav učinak na sve vrste mortaliteta. Broj ponavljenih hospitalizacija zbog ZS-a ili drugih uzroka vjerovatno se smanjuje uz individualne intervencije. Kod intervencija temeljenih na kliničkom pručenju nema razlike u ponavljanjem hospitalizacijama zbog ZS-a ili te intervencije vjerovatno mogu malo napraviti, kao i kod ponavljanja hospitalizacija zbog bilo kojega drugog uzroka. Multidisciplinarne intervencije mogu smanjiti rizik od ponavljanja hospitalizacije zbog ZS-a ili bilo kojega drugog uzroka. Nisu nađeni dostatni podaci o neželjenim učincima, a i zaključak o kvaliteti života u ovim ispitivanjima nije siguran zbog lošije kvalitete podataka. Zbog različitih lokacija i vremena provođenja, nije bilo moguće napraviti kvalitetnu analizu troškova i učinkovitosti.

Poboljšanje kvalitete života vrlo je važno, no o tome se malo izvještava. Kvalitetnije izvještavanje o kvaliteti života istaknutih u budućim ispitivanjima pružilo bi snažnije dokaze za izhode bitne bolesnicima.

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