Godina 2022. u kardiovaskularnoj medicini: 10 najboljih radova iz područja zatajivanja srca i kardiomiopatija

The year in cardiovascular medicine 2022: the top 10 papers in heart failure and cardiomyopathies

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Godina 2022. bila je posebno izazovna u području zatajivanja srca (ZS). U kratkom izvještaju koji slijedi naglasit ćemo neke od najznačajnijih i najprovokativnijih publikacija na ovom području.

Natrij-glukoza kotransporter 2 (SGLT2) inhibitori postaju jedan od najvažnijih načina liječenja u bolesnika s kardiorenalnim sindromom. Postoje novi izazovi, primjerice jesu li SGLT2 inhibitori jednako učinkoviti u bolesnika s akutnim ZS-om ili kod ZS-a s istisnom frakcijom lijeve klijetke (LVEF) >40 %, ili u bolesnika s poboljšanom LVEF. Istraživanje *EMPULSE (The Study to Test the Effect of Empagliflozinin Patients Who Are in Hospital for Acute Heart Failure*; NCT04157751) testiralo je učinak empagliflozina u bolesnika koji su hospitalizirani zbog akutnog ZS-a. U

The year of 2022 has been an exciting year in heart failure (HF). In this brief report, we will highlight some of the most provocative and impactful papers in the field.

Sodium–glucose co-transporter 2 (SGLT2) inhibitors are becoming one of the main treatments for patients with cardiorenal disease. Some uncertainties remained, e.g. if SGLT2 inhibitors were effective in patients with acute HF (AHF), or in HF with a left ventricular ejection fraction (LVEF)>40%, or in patients with improved LVEF. The Study to Test the Effect of Empagliflozin in Patients Who Are in Hospital for Acute Heart Failure (EMPULSE; NCT04157751) trial enrolled 530 patients with acute de novo or decompensated HF to receive empagliflozin 10 mg once daily or placebo.[1] The unique aspect of EMPULSE was

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istraživanje je uključeno 530 bolesnika s akutnim novonastalim ZS-om ili dekompenziranim stadijem ZS-a, na empagliflozin 10 mg na dan ili placebo[1]. Važan dio istraživanja *EMPULSE* jest randomizacija bolesnika u bolnici, kada je bila postignuta stabilizacija kliničkoga stanja (median vremena do randomizacije: 3 dana) uz procjenu ishoda do 90. dana. Većina bolesnika liječenih empagliflozinom pokazala je kliničko poboljšanje u usporedbi s placebom (procijenjeno kao „win" omjer). Postiglo se znatno smanjenje mortaliteta i ponavljane hospitalizacije zbog ZS-a.

Istraživanje *DELIVER (The Dapagliflozin Evaluation to Improve the LIVEs of Patients with Preserved Ejection Fraction Heart Failure*; NCT03619213) ispitivalo je dapagliflozin u smislu procjene poboljšanja kliničkoga stanja bolesnika s očuvanom LVEF. Istraživanje je bilo randomizirano, dvostruko slijepo, a uključilo je 6263 bolesnika s kroničnim simptomatskim ZS-om, LVEF-om >40 % i povišenim vrijednostima natriuretskih peptida. Uspoređivan je učinak dapagliflozina, 10 mg jedanput na dan naspram placeba, kao dodatak na standardnu terapiju[2]. Nakon praćenja (medijan 28 mjeseci) primarni ishod (kardiovaskularna smrt ili hospitalizacija zbog ZS-a) zabilježen je u 16,4 % bolesnika u skupini na dapagliflozinu i u 19,5 % u skupini na placebu (HR 0,82; 95 % CI: 0,73 – 0,92; P <0,001, Panel A). Rezultati su bili slični u unaprijed određenim podskupinama. Učestalost neželjenih događaja povezana s prekidom liječenja (zbog deplecije volumena i hipoglikemija) bila je usporediva u objema skupinama.

Skupna analiza podataka bolesnika iz istraživanja *DAPA-HF* (NCT03036124) i *DELIVER* (n = 11 007) pokazala je sličan povoljan učinak dapagliflozina, neovisno o vrijednosti LVEF-a[3]. Dapagliflozin je smanjio rizik od zajedničkog ishoda (hospitalizacije zbog ZS-a ili KV smrti; Panel B), kardiovaskularne smrti (HR 0,86; 95 % CI: 0,76 – 0,97; P = 0,01), ukupne smrtnosti (HR 0,90; 95 % CI: 0,82 – 0,99; P = 0,03), ukupne hospitalizacije zbog ZS-a (HR 0,71; 95 % CI: 0,65 – 0,78; P <0,001), kao i MACE-a (HR 0,89; 95 % CI: 0,80 – 0,99; P = 0,02). U ovoj metaanalizi, nije uočena razlika učinaka dapagliflozina s obzirom na vrijednosti LVEF-a.

Nekoliko je publikacija proučavalo diurezu, renalnu funkciju, natrij i kalij.

U vezi s restrikcijom soli u ZS-u raspravlja se godinama, te je u povodu toga dizajnirano istraživanje o ZS-u uz primjenu dijetetičkih intervencija uz Na <100 mmola (*Study of Dietary Intervention under 100 mmol in Heart Failure; SODIUM-HF*) kako bi se testiralo smanjuju li manje količine soli u prehrani incidenciju kliničkih događaja u budućnosti[4]. Spomenuto istraživanje uključilo je 806 bolesnika s kroničnim ZS-om koji su liječeni sukladno smjernicama, a bili su randomizirani na one koji dobivaju uobičajnu terapiju u skladu s lokalnim smjernicama i na one koji imaju propisanu dijetu s niskim razinama soli (NRS) od <100 mmola (što je <1500 mg/dan). Medijan uzimanja soli smanjen je s 2286 mg/dan (interkvartilni raspon 1653 – 3005) na 1658 mg/dan (1301 – 2189) u grupi s NRS-om, te s 2119 mg/dan (1673 – 2804) na 2073 mg/dan (1541 – 2900) u grupi na uobičajenom liječenju. Nakon 12 mjeseci primarni zajednički ishod (prijem u bolnicu zbog kardiovaskularnih bolesti, posjeta hitnoj službi zbog kardiovaskularnih razloga i ukupna smrtnost) zabilježen je u 15 % bolesnika u NRS skupini i u 17 % onih na uobičajnom liječenju (HR 0,89; 95 % CI: 0,63 – 1,26; P = 0,53). Dijetetičke intervencije uz redukciju

that patients were randomized in hospital, when clinically stabilized (median time to randomization: 3 days), and were treated for up to 90 days. More patients treated with empagliflozin had clinical benefits compared with placebo (this was assessed by a 'win' ratio). Mortality and HF readmissions were also reduced.

The Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER, NCT03619213) study was a randomized double-blind clinical trial in 6263 patients with chronic symptomatic HF, LVEF>40%, and elevated natriuretic peptides comparing the effect of dapagliflozin 10 mg once daily vs. placebo, in addition to standard of care.[2] After a median follow-up of 28 months, the primary outcome [death from cardiovascular (CV) causes or HF hospital admissions] occurred in 16.4% in the dapagliflozin group and in 19.5% in the placebo group [hazard ratio (HR) 0.82; 95% confidence interval (95% CI): 0.73–0.92; P<0.001, Panel A]. Findings were similar in prespecified subgroups. The frequency of adverse events leading to treatment discontinuation, related to volume depletion, and hypoglycaemia were similar between groups.

A prespecified patient-level pooled analysis (n=11 007) of the DAPA-HF (NCT03036124) and DELIVER trials[3] found that the benefits of dapagliflozin were similar regardless of LVEF. Dapagliflozin reduced the risk of the composite of HF hospitalizations or CV death (Panel B), and of CV death alone (HR 0.86; 95% CI: 0.76–0.97; P=0.01), death from any cause (HR 0.90; 95% CI: 0.82–0.99; P=0.03), total hospitalizations for HF (HR 0.71; 95% CI: 0.65–0.78; P< 0.001), and MACE (HR 0.89; 95% CI: 0.80–0.99; P=0.02). In this patient-level meta-analysis, there was no evidence that the effects of dapagliflozin differed by LVEF.

Several papers addressed the issue of diuresis, renal function, sodium, and potassium.

The issue of sodium restriction in HF has been disputed for long, and the study of dietary intervention under 100 mmol in heart failure (SODIUM-HF) was designed to test whether or not a reduction in dietary sodium reduces the incidence of future clinical events.[4] SODIUM-HF enrolled 806 patients with chronic HF receiving guidelinedirected medical treatment, and randomized them to either usual care according to local guidelines or a low sodium diet (LSD) of <100 mmol (this is <1500 mg/day). The median sodium intake decreased from 2286 mg/day (interquartile range 1653–3005) to 1658 mg/day (1301–2189) in the low sodium group and from 2119 mg/day (1673–2804) to 2073 mg/day (1541–2900) in the usual care group. By 12 months, the primary composite endpoint of CV-related admission to hospital, CV-related emergency department visit, or all-cause death had occurred in 15% of patients in the LSD group and 17% in the usual care group (HR 0.89; 95% CI: 0.63–1.26; P= 0.53). So, a dietary intervention to reduce sodium intake does not reduce clinical events.

Patiromer is a potassium lowering agent, and the Patiromer for the Management of Hyperkalemia in Participants Receiving RAASi Medications for the Treatment of Heart Failure (DIAMOND, NCT03888066) trial investigated the effects of patiromer on serum potassium level, and if its use would enable target doses of renin–angiotensin– aldosterone system inhibitors (RAASi) use in patients with HFrEF.[5] A total of 1195 patients were enrolled during the run-in phase with patiromer and optimization of RAASi therapy [≥50% recom-

uzimanja soli nisu dovele do smanjenja neželjenih kliničkih događaja.

Patiromer, lijek koji snizuje razinu kalija (*Patiromer for the Management of Hyperkalemia in Participants receiving RAASi Medications for the Treatment of Heart Failure*; istraživanje *DIAMOND*; NCT03888066) istraživan je u bolesnika sa ZS-om koji primaju renin-angiotenzin-aldosteronske inhibitore (RAASi). Promatrao se učinak patiromera na serumske razine kalija, kao i to može li uporaba omogućiti primjenu ciljne doze RAAS inhibitora u bolesnika s HFrEF-om.[5] Ukupno je bilo uključeno 1195 bolesnika tijekom početne faze na patiromeru, uz optimiziranje liječenja RAASi (≥50 % preporučene doze RAASi i 50 mg antagonista mineralokortikoidnih receptor antagonista – MRA); navedeno je bilo realizirano u 878 (84,6 %) bolesnika koji su bili randomizirani 1 : 1. Na kraju liječenja, prilagođena srednja promjena u vrijednosti kalija iznosila je +0,03 mmol/L u skupini na patiromeru i za +0,13 mmol/L u skupini na placebu (razlika: −0,10 (95 % CI −0.13, −0.07), P <0,001). Navedeno je bilo praćeno manjim rizikom od hiperkalemije (>5,5 mmol/L) i manjom redukcijom MRA doze. Većina bolesnika s hiperkalemijom, koji su trebali smanjenje doze RAASi ili MRA, mogli su tolerirati odgovarajuće doze RAASi ili MRA tijekom istraživanja *DIAMOND*. U svakom slučaju, patiromer omogućuje adekvatnu titraciju RAASi i MRA u bolesnika s hiperkalemijom, premda je broj bolesnika koje je potrebno liječiti kako bi se prevenirao loš klinički ishod ovom strategijom prilično velik.

Rezistencija na diuretike drugi je klinički izazov koji je istraživan u dvama zanimljivim istraživanjima. Istraživanje *ADVORI* (*Acetazolamide in Acute Decompensated heart Failure with Volume Overload*)[6] u akutnom ZS-u sa znakovima prekomjernog volmena evaluiralo je smanjuje li acetazolamid (inhibitor karboanhidraze) reapsorpciju natrija u proksimalnom tubulu, osim uzimanja diuretika Henleove petlje. Ukupno 519 bolesnika s akutnim ZS-om i kliničkim znakovima prekomjernog volumena i vrijednostima NTproBNPa >1000 pg/mL, bilo je randomizirano u skupinu na acetazolamidu intravenski (500 mg jedanput na dan) ili na placebo, uz standardnu intravensku diuretsku terapiju diureticima Henleove petlje. Uspješna se dekongestija češće postizala u skupini na acetazolamidu u usporedbi s placebom (omjer rizika – RR 1,46, 95 % CI; 1,17 – 1,82; P <0,001, Panel C). Liječenje acetazolamidom bilo je povezano s većom diurezom i natriurezom, što sveukupno čini bolju diuretsku učinkovitost. No nije došlo do promjena u simptomima, tjelesnoj težini i EuroQoL ishodima. Incidencija pogoršanja bubrežne funkcije, hipokalemija, hipotenzija, kao i neželjeni događaji bili su slični u objema grupama. Ovi podatci znatno pridonose saznanjima o primjeni diuretika u akutnom ZS-u.

Istraživanje *CLOROTIC (Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure*; NCT01647932)[7] ispitivalo je je li dodatak hidroklorotiazida (HCT) intravenskom furosemidu sigurna i učinkovita strategija za poboljšanje diuretskog odgovora u bolesnika s akutnim ZS-om. Sveukupno 230 bolesnika (48 % žena, 83 godine) bilo je randomizirano na HCT ili na placebo. Skupina na HCT-u izgubila je više tjelesne težine nakon 72 sata (–2,3 *vs.* –1,5 kg; –1,14 (95 % CI –1,84 do –0,42); P = 0,002), no nije bilo signifikantne razlike u tegobama od otežanog disanja. Mortalitet ili rehospitalizacije zbog ZS-a bili su slični između skupina na HCT-u i placebu. U skupini na HCT-u

mended dose of RAASi and 50 mg of mineralocorticoid receptor antagonist (MRA)]; this was achieved in 878 (84.6%) of the patients who were 1:1 randomized. At the end of the treatment, the adjusted mean change in potassium was +0.03 mmol/L in the patiromer group and +0.13 mmol/L in the placebo group [difference: −0.10 (95% CI −0.13, −0.07), P<0.001]. This was accompanied by lower risk of hyperkalaemia (>5.5 mmol/L) and less reductions in MRA dose. Strikingly, a large proportion of the patients with hyperkalaemia in the past whose RAASi or MRA was downtitrated could tolerate adequate dosages of RAASi and/or MRA during the run-in phase of the DIAMOND trial. In any way, patiromer enables adequate titration of RAASi and MRA in patients with hyperkalaemia, although the number needed to treat to prevent hard clinical outcomes by this strategy appears to be rather high.

Diuretic resistance is another clinical dilemma which was addressed by two interesting trials. The Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR) trial[6] evaluated if acetazolamide, a carbonic anhydrase inhibitor, reduces proximal tubular sodium reabsorption, on top of loop diuretics in patients with AHF; 519 AHF patients and clinical signs of volume overload and an NT-proBNP level of more than 1000 pg/mL were randomized to either intravenous acetazolamide (500 mg once daily) or placebo added to standardized intravenous loop diuretics. Successful decongestion was more often achieved in the acetazolamide group compared with the placebo group [risk ratio (RR) 1.46, 95% CI: 1.17–1.82; P<0.001; Panel C]. Acetazolamide treatment was associated with higher cumulative urine output and natriuresis, findings consistent with better diuretic efficiency. However, neither changes in symptoms, nor weight, nor the EuroQoL outcomes were reported and may complement the published data. The incidence of worsening kidney function, hypokalaemia, hypotension, and adverse events was similar in the two groups. These data likely will shift the standard diuretic regimen in AHF.

The Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC trial; NCT01647932)[7] evaluated if addition of hydrochlorothiazide (HCT) to intravenous furosemide is a safe and effective strategy for improving diuretic response in patients with AHF. In total, 230 patients (48% women, 83 years) were randomized to HCT or placebo; those on HCT lost more weight at 72 h [−2.3 vs.−1.5 kg; −1.14 (95% CI −1.84 to −0.42); P=0.002], but there were no significant differences in patient-reported dyspnoea. Mortality or HF rehospitalization rates were similar between HCT and placebo. Patients with HCT more often had a significant increase in creatinine (46.5% vs. 17.2%; P<0.001).

Several other interesting articles were published.

First, the long-standing dispute about whether or not patients with ischaemic cardiomyopathy may benefit from revascularization by percutaneous coronary intervention (PCI), when compared with optimal medical therapy (OMT) (i.e. individually adjusted pharmacologic and device therapy for HF), was addressed by the Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure (REVIVED-BCIS2; NCT01920048).[8] Patients with an LVEF of 35% or less, extensive coronary artery disease that could be treated by PCI, and demonstrable myocardial viability were randomized to either PCI plus OMT (PCI group) orOMT

češće je registrirano znatno povećanje vrijednosti kreatinina (46,5 % *vs.* 17,2 %, P <0,001).

Publicirano je još nekoliko drugih zanimljivih istraživanja.

Prije svega, dugo se razmatra mogu li bolesnici s ishemijskom kardiomiopatijom imati koristi od revaskularizacije perkutanom koronarnom intervencijom (PCI) u usporedbi s optimalnom medikamentnom terapijom (OMT; podrazumijeva individualno prilagođenu farmakološku terapiju i terapiju uređajima). Sve je to bilo obuhvaćeno istraživanjem *REVIVED-BCIS2* (Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure; NCT01920048)[8]. Bolesnici s LVEF-om od 35 % ili manje i značajnom koronarnom bolesti srca koja je mogla biti liječena PCI-jem i dokazanom vijabilnosti miokarda, bili su randomizirani na skupinu PCI uz OMT (PCI skupina) i OMT skupinu. Ukupno je 347 bolesnika bilo raspoređeno u PCI skupinu, a 353 u OMT skupinu. Tijekom medijana od 41 mjesec primarni ishod (ukupna smrtnost ili hospitalizacija zbog ZS-a) zabilježen je u 37,2 % bolesnika u PCI skupini i u 38,0 % bolesnika u OMT skupini (HR 0,99; 95 % CI: 0,78-1,27; P = 0,96; Panel D). LVEF je bila slična u objema skupinama u 6. i 12. mjesecu. Prema tome, revaskularizacija primjenom PCI-ja nije pokazala pozitivan rezultat u promatranoj skupini bolesnika s obzirom na primjenu samo medikamentne terapije.

Konačno, objavljene su dvije zanimljive publikacije o titraciji lijekova u ZS-u. Donedavno su Smjernice preporučivale započinjanje terapije za liječenje ZS-a u postupnom nizu, uz sporo i kontrolirano povećavanje doze pojedinačnih lijekova. No najnovije Smjernice preporučuju da se četiri osnove grupe lijekova ubrzano titriraju; ipak, redosljed i brzina titracije nije precizirana.

Prvo istraživanje[9] opisuje retrospektivnu analizu podataka o mortalitetu iz 6 istraživanja o ZS-u: *SOLVD-Treatment* (inhibitor angiotenzin-konvertirajućeg enzima, enalapril), *MERIT-HF* (beta-blokator, metoprolol), *EMPHASIS-HF* (MRA, eplerenon), *PARADIGM-HF* (angiotenzin receptor-neprilizin inhibicija), *DAPA-HF* (SGLT2 inhibicija, dapagliflozin) i *CHARM* (angiotenzin receptor blokator, kandesartan). Autori su proučavali potencijalnu redukciju KV događaja koji bi se mogli očekivati uz pojačanu titraciju konvencionalnog slijeda lijekova (temeljeno na kronologiji studija) i uspoređivali s ubrzanom titracijom, koristeći se liječenjem različitim redoslijedom, s obzirom na sadašnje konvencionalne preporuke. Doista, ubrzana je titracija bila povezana s manje hospitalizacija zbog ZS-a ili KV smrti. Nadalje, identificiran je optimalan alternativni slijed lijekova, uz prijedlog da SGLT2 i MRA mogu biti prva dva primijenjena lijeka.

U istraživanju *STRONG-HF (Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies*, NCT03412201)[10] bolesnici hospitalizirani zbog akutnog ZS-a bili su randomizirani na one koji nisu liječeni punom dozom smjernicama preporučenih lijekova i na one koji su liječeni uobičajenom ili visokointenziviranom terapijom (HIC). HIC je bio definiran kao povećavanje doze lijekova do maksimalne, 100 % preporučene doze, unutar 2 tjedna od otpusta, uz 4 planirane ambulantne kontrole tijekom dva mjeseca od otpusta, kako bi se pobliže pratili klinički status, laboratorijski nalazi i biomarkeri. Primarni ciljni ishod bili su ponovna hospitalizacija zbog ZS-a unutar 180 dana ili ukupna smrtnost. Sveukupno je 1078 bolesnika bilo randomizirano u HIC skupinu (n = 542) ili u skupinu s uobičajnom terapijom (n = 536). Ukupno je 1078 bolesnika bilo randomizirano u HIC skupinu (n = 542) ili u skupinu s uobičajnom terapijom (n = 536). Sveukupno je 1078 bolesnika bilo randomizirano u HIC skupinu (n = 542) ili u skupinu s uobičajnom terapijom (n = 536). Sveukupno je 1078 bolesnika bilo randomizirano u HIC skupinu (n = 542) ili u skupinu s uobičajnom terapijom (n = alone. Totally, 347were assigned to the PCI group and 353 to the OMT group. Over a median of 41 months, a primary outcome (death from any cause or HF hospitalization) occurred in 37.2% in the PCI group and in 38.0% in the OMT group (HR 0.99; 95% CI: 0.78–1.27; P = 0.96; Panel D). The LVEF was similar in the two groups at 6 and 12 months. So, revascularization by PCI has no benefit in these patients on top of medical therapy.

Finally, two interesting articles addressed how drug titration in patients with HF may be handled. Until recently, the guidelines recommended initiating therapy in patients with HF in a historical sequence, with slow and controlled up-titration of individual classes of drugs. However, the newest guidelines state that four classes of drugs should be titrated on a faster schedule; however, the order and speed of titration remained unaddressed.

A first study[9] to address this was a retrospective study analysing data from six major mortality trials in HF: the SOLVD-Treatment trial (angiotensin-converting enzyme inhibition, enalapril), the MERIT-HF trial (beta-blockade, metoprolol), EMPHASIS-HF (MRA, eplerenone), the PARADIGM-HF trial (angiotensin receptor–neprilysin inhibition), DAPA-HF (SGLT2 inhibition, dapagliflozin), and CHARM (angiotensin receptor blocker, candesartan). The authors modelled the potential reductions in CV events that might be expected from more rapid uptitration in the conventional order (based on a chronology of trials), and compared this to accelerated up-titration, using treatments in different orders than currently is conventional. Indeed, a rapid up-titration schedule was associated with fewer HF hospitalization or CV death. Furthermore, an optimal 'alternative' sequence of drugs was identified, which proposed SGLT2i and an MRA as the first two therapies.

A second study addressing this pressing issue was the Safety, Tolerability and Efficacy of Rapid Optimization, Helped by NT-proBNP testinG, of Heart Failure Therapies (STRONG-HF; NCT03412201).[10] STRONG-HF randomized patients who were admitted to the hospital with AHF, who were not treated with full doses of guideline-directed drug treatment, to usual care or high-intensity care (HIC). HIC was defined by the up-titration of treatments to 100% of recommended doses within 2 weeks of discharge, with four scheduled outpatient visits over the 2 months after discharge, to closely monitor clinical status, laboratory values, and biomarkers. The primary endpoint was 180-day readmission for HF or all-cause death. In total, 1078 patients were randomized to HIC (n=542) or usual care (n=536). The study was stopped prematurely by the DSMB because of greater than expected between-group differences. A higher proportion of HIC patients had been up-titrated to full doses of prescribed drugs. HF readmission or all-cause death up to day 180 occurred in 74 (15.2%) of 506 patients in the HIC group and 109 (23.3%) of 502 patients in the usual care group (difference: 8.1%; RR 0.66, 95% CI: 0.50–0.86). Patients receiving HIC thus ended up having both more medical attention and visits as well as higher dosages of drugs—it remains uncertain what part of the benefit is explained by what element. More adverse events by 90 days occurred in the HIC group (41%) than in the usual care group (29%), but similar incidences of serious adverse events were reported in each group.

Overall, these two trials provide strong support for accelerated titration of guideline-directed drug treatment, while the order of drugs installed does not need to be based on historical grounds.

536). Istraživanje je bilo ranije prekinuto (od odbora za provjeru podataka i sigurnosti) zbog veće od očekivane razlike između skupina. Više bolesnika u skupini HIC bilo je titrirano do pune doze preporučenih lijekova. Ponovna hospitalizacija zbog ZS-a ili ukupna smrtnost do 180. dana promatranja zabilježeni su u 74 (15,2 %) od 506 ispitanika u HIC skupini i 109 (23,2%) od 502 bolesnika u skupini koja je imala uobičajenu terapiju (razlika: 8,1 %, RR 0,66, 95 % CI: 0.50 – 0,86). Bolesnici u HIC skupini imali više kontrola, kao i veće doze lijekova, a nije dokraja razjašnjeno koji je dio važniji u objašnjavanju dobrobiti glede ishoda. Više je neželjenih događaja bilo zabilježeno 90-og dana u skupini HIC nego u onoj koja je imala uobičajno liječenje (29 %), a uočena je slična incidencija ozbiljnih neželjenih događaja u objema skupinama.

Sveukupno, spomenuta dva istraživanja pružaju dokaze u smislu ubrzane titracije smjernicama preporučenih lijekova, dok redoslijed davanja lijekova ne treba biti temeljen na povijesnim načelima.

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