Godina 2015. u kardiologiji: srčano zatajivanje

The year in cardiology 2015: heart failure

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Uvod

Tijekom 2015. godine predstavljeni su i objavljeni rezultati mnogih studija o zatajivanju srca (ZS) sa smanjenom ili održanom sistoličkom funkcijom lijeve klijetke. Većina ih je bila neutralna te nije dokazala dobrobit na ishode primjenom testiranih lijekova ili postupaka. Unatoč tomu, studije donose nove informacije važne za otkriće novih lijekova ili postupaka u liječenju ZS-a.

Adaptivna servoventilacija u zatajivanju srca i središnja apneja u snu: je li štetna?

Poremećaji disanja tijekom spavanja učestali su u bolesnika sa ZS-om i smanjenom istisnom frakcijom (EF). Opisana su dva različita tipa abnormalnosti: opstruktivna apneja i centralna apneja u snu. Učestalost središnje apneje u snu, koja se može očitovati kao Cheyne-Stokesovo disanje, povećava se s težinom stupnja ZS-a i povezano je s lošim ishodima.

Svrha SERVE-HF istraživanja bila je da se procijene učinci adaptivne servoventilacije (ASV) koja pruža servokontroliranu potporu udisajnoga tlaka povrh pozitivnoga izdisajnog tlaka u pacijenata s umjerenim do ozbiljnim stupnjem ZS-a i EF < 45 % koji su imali većinom centralnu apneju u snu.[1] U ovoj je studiji 1325 pacijenata bilo randomizirano u skupine liječene ASV-om (666) i kontrolnom terapijom (659). Pacijenti su većinom bili

Preamble

A number of studies conducted both in heart failure with reduced and with preserved ejection fraction were presented and published in 2015. Most of them were neutral and did not demonstrate any benefit on outcomes of the drugs/procedures tested. Nevertheless, they bring important new information on the search for new drugs or procedures in the management of heart failure.

Adaptive servo-ventilation in heart failure and central sleep apnoea: is it harmful?

Sleep-disordered breathing is common in patients with heart failure and reduced ejection fraction. Two different types of abnormality have been described: obstructive sleep apnoea and central sleep apnoea. The prevalence of central sleep apnoea, which may manifest as Cheynes–Stokes respiration, increases with the severity of heart failure and this condition is associated with poor outcomes.

The purpose of SERVE-HF was to assess the effects of adaptive servo-ventilation (ASV) that delivers servo-controlled inspiratory pressure support on top of expiratory positive airway pressure in patients with moderate to severe heart failure and an ejection of <45% who had predominantly central sleep apnoea.[1] In this tri-

u III. stupnju ZS-a prema *New York Heart Association* (NYHA) klasifikaciji i dobro liječeni preporučenim lijekovima. Učestalost primarnih ishoda koji su bili ukupna smrtnosti, kardiovaskularne intervencije koja je spasila život ili neplanirane hospitalizacije zbog ZS-a nije se razlikovala u tim dvjema skupinama (HR = 1,13; 95 % CI, 0,97 – 1,31; *P* = 0,10). Iznenađujuće je bilo opažanje znatnog povećanja ukupne (HR = 1,28; 95 % CI, 1,06–1,55; *P* = 0,01) i kardiovaskularne smrtnosti (HR = 1,34; 95% CI, 1,09–1,65; *P* = 0,006) u skupini na ASV-u. Zaključci SERVE-HF nisu sukladni ranijim manjim studijama koje su pokazivale poboljšanje funkcije lijeve klijetke, kvalitete života i smrtnosti.

Jedno od mogućih objašnjenja za povećanje kardiovaskularne smrtnosti jest da centralna apneja u snu može biti kompenzatorni mehanizam te stoga smanjenje ovoga adaptivnog uzorka disanja putem ASV-a može biti škodljivo. Drugo objašnjenje koje su predložili *Cowie i sur.* jest da primjena pozitivnoga tlaka u dišnim putovima može narušiti kardiološku funkciju, posebice u pacijenata s niskim plućnim kapilarnim tlakom. Zbog ovoga će biti važno odrediti točno vrijeme smrti te je li se smrtni slučaj zbio dok su pacijenti bili pod AVS-om kako bi se mogli utvrditi potencijalni štetni mehanizmi.

Važna posljedica negativnih rezultata SERVE-HF-a jest da se ovaj postupak više ne bi trebao preporučivati pacijentima sa ZS-om i smanjenom EF te centralnom apnejom u snu te bi trebala biti obustaviti u pacijenata koji se trenutačno liječe ovom metodom. Međutim, ovo ne vrijedi za opstruktivnu apneju u snu.

Jesu li druge metode smanjena Cheyne-Stokesova disanja poput stimulacije freničnog živca korisne ili štetne, ostaje neodgovoreno pitanje dok ne postanu dostupni rezultati trenutačne studije.

Oralni hipoglikemici i rizik od zatajivanja srca: novi ohrabrujući rezultati

Inhibitori dipeptidilpeptidaze 4 (DPP-4 inhibitori) već se nekoliko godina uporabljuju u liječenju dijabetesa tipa 2. Studija SAVOR-TIMI 53, objavljena 2013., potaknula je zabrinutost za sigurnost uporabe ove klase lijekova zbog pojavnosti slučajeva ZS-a.[2] Ta velika studija koja je uključivala pacijente s dijabetesom i prethodnim kardiovaskularnim događajima ili s visokim kardiovaskularnim rizikom pokazala je da je općenita kardiovaskularna sigurnost saksagliptina dobra, osim 27 %-tnog povećanja rizika hospitalizacije zbog nastupa prve

al, 1325 patients were enrolled and randomized to ASV (666) or to control therapy (659). Patients were predominantly in New York Heart Association Class III and were well treated by recommended therapies. The incidence of the primary endpoint made of the composite of death of any cause, lifesaving cardiovascular intervention, or unplanned hospitalization for heart failure did not differ significantly between the two groups (HR = 1.13; 95% CI, 0.97–1.31; *P* = 0.10). The surprise was the observation of a significant increase of all-cause mortality (HR = 1.28; 95% CI, 1.06–1.55; *P* = 0.01) and of cardiovascular mortality (HR = 1.34; 95% CI, 1.09–1.65; *P* = 0.006) in the ASV group. The findings of SERVE-HF contrast with evidence from earlier smaller studies that suggested an improvement in left ventricular function, quality of life, and mortality.

One potential explanation for the increase in cardiovascular mortality is that central sleep apnoea may be a compensatory mechanism, and therefore reducing this adaptive respiratory pattern by ASV may be detrimental. The other explanation put forward by Cowie *et al.* is that the application of positive airway pressure may impair cardiac function, in particular, in patients with low pulmonary capillary wedge pressure. The timing of death and whether the fatal events occurred while patients were under ASV will be therefore important to determine the potential mechanism of harm.

One important implication of the negative results of SERVE-HF is that this procedure should not be recommended anymore for patients with heart failure and reduced ejection fraction and central sleep apnoea and stopped in those patients currently treated by this procedure. This, however, does not apply to obstructive sleep apnoea.

Whether other techniques diminishing Cheynes–Stokes respiration such as phrenic nerve stimulation are beneficial or harmful remains an open question until the results of the ongoing trial testing phrenic nerve stimulation are available.

Glucose-lowering agents and risk of heart failure: new and reassuring results

Dipeptidyl peptidase 4 inhibitors (DPP4 inhibitors) have been used for several years in the management of type 2 diabetes mellitus. In 2013, the publication of SAVOR-TIMI 53 raised concern on the safety of this class regarding the occurrence of heart failure events.[2] This large outcome trial including patients with diabetes mellitus and a previous cardiovascular event or at high cardiovascular risk showed that the overall

TABLE 1. Heart failure events in recent trials with glucose-lowering drugs.

Study	Drug	No. of Patients	Follow-up (years)	Heart failure (HR) hospitalization	P-value
SAVOR	Saxagliptin	16 492	2.1	1.27 (95% CI, 1.07–1.51)	0.007
EXAMINE	Alogliptin	5380	1.5	1.07 (95% CI, 0.79–1.46)	0.66
TECOS	Sitagliptin	14 671	3.0	1.00 (95% CI, 0.83–1.20)	0.98
EMPA-REG	Empagliflozin	7020	3.1	0.65 (95% CI, 0.50–0.85)	0.002

epizode ZS-a. Nije postojalo biološki uvjerljivo objašnjenje ovog opažanja. Ipak, ovo je još više potaknulo zabrinutost za moguću štetnost, pogotovo nakon rezultata EXAMINE studije koji su u dijabetičara s akutnim koronarnim sindromom dokazala neznačajan signal povišenog rizika od ZS-a s drugim DPP-4 inhibitorom, alogliptinom (**tablica 1**).[3]

Objavljivanje velike studije TECOS koja je uključivala 14 671 pacijenta bila je dugo očekivano.[4] U studiju su bili uključeni dijabetičari tipa 2, stariji od 50 godina, s dokazanom kardiovaskularnom bolesti i početnom vrijednosti HbA1C-a od 6,5 do 8 %. Pacijenti su bili randomizirani u skupinu liječenu s DPP-4 inhibitorom sitagliptinom ili u kontrolnu skupinu.

Nakon 3 godine praćenja nije registrirana razlika u učestalosti zajedničkog ishoda koji je uključivao kardiovaskularnu smrtnost, nesmrtonosni infarkt miokarda, nesmrtonosni moždani udar ili hospitalizacije zbog nestabilne angine pektoris (HR = 0,98; 95 % CI, 0,88 – 1,09; *P* < 0,001 za neinferiornost). Značajno je da je učestalost ZS-a bila slična u objema skupinama s omjerom rizika od 1,00 (95 % CI, 0,83 – 1,20; *P* = 0,98). Objašnjenje različitog učinka sitagliptina i saksagliptina na slučajeve ZS-a ostaje nejasno: malo je vjerojatno da su razlike među uključenim pacijentima imale bitnu ulogu jer je klinički profil pacijenata bio prilično sličan. Moguće su objašnjenje razlike u afinitetu dvaju inhibitora prema raznim supstratima DDP-4. Konačno, u ovako velikoj studiji ne može se izuzeti uloga slučajnosti.

Kakvo god bilo objašnjenje, rezultati ovako velikih studija u bolesnika s dijabetesom tipa 2 isključuju učinak klase inhibitora DPP-4 na pojavnost ZS-a i stoga su obećavajući glede sigurnosti sitagliptina u pacijenata sa ZS-om ili koji u onih s visokim rizikom od ZS-a.

Još jedna studija, EMPA-REG OUTCOME, testirala je dvije doze inhibitorako-transportera 2 natrij glukoze empagliflozina naspram placeba u 7020 pacijenata s dijabetesom tipa 2 i visokim kardiovaskularnim rizikom.[5] Nakon medijana praćenja od 3,1 godine u skupini na empagliflozinu registrirano je znatno (za 14 %) smanjenje primarnoga zajedničkog ishoda sastavljenog od kardiovaskularne smrtnosti, nesmrtonosnog infarkta miokarda ili nesmrtonosnog moždanog udara. Zanimljivo je da su dva sekundarna ishoda (hospitalizacija zbog ZS-a i kombinirani ishod hospitalizacije zbog ZS-a i kardiovaskularna smrtnost), također bili znatno smanjeni za 35 % (*P* = 0,002), odnosno 34 % (<0,01), što upućuje na to da je ovaj novi antidijabetik dodan standardnoj terapiji u bolenika s dijabetesom tipa 2 nije samo siguran nego i koristan za prevenciju hospitalizacije zbog ZS-a.

Liječenje zatajivanja srca s održanom sistoličkom funkcijom i dalje ostaje klinička dilema

Farmakološko liječenje ZS-a s održanom EF (HFpEF) i dalje ostaje izazov i nijedan lijek nije pokazao jasnu dobrobit glede pobola i smrtnosti u tih pacijenata (**slika 1**).

Istraživanje SUPPORT analiziralo je smanjuje li primjena liječenja olmesartanom (blokator angiotenzinskih receptora) smrtnost i pobol u hipertoničara s kroničnim ZS-om liječeni-

cardiovascular safety of saxagliptin was good, except a 27% increase in the risk of the first event worsening heart failure hospitalization. There was no biological plausible explanation for this observation. Nevertheless, this raised concern on potential harm all the more as another trial EXAMINE conducted in patients with diabetes mellitus and presenting with an acute coronary syndrome suggested a non-significant signal for increased risk of heart failure with another DPP4 inhibitor, alogliptin (**Table 1**).[3]

The publication of TECOS, another mega trial including 14 671 patients was therefore long awaited.[4] Patients included had type 2 diabetes mellitus, were 50 years of age or more, and had an established cardiovascular disease and a baseline HbA1C of 6.5–8%. They were randomized to either the DPP4 inhibitor sitagliptin or to control treatment.

After 3 years of follow-up, no difference was observed in the occurrence of the composite endpoint of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina (HR = 0.98; 95% CI, 0.88–1.09; *P* < 0.001 for non-inferiority). Importantly, the incidence of heart failure was similar in the two arms with a hazard ratio of 1.00 (95% CI, 0.83–1.20; *P* = 0.98). The explanation for the differential effect of sitagliptin and of saxagliptin on heart failure events remain uncertain: differences in populations enrolled in the two trials are unlikely to play a role since the clinical profile of the patients were rather similar. Differences in affinity of the two inhibitors to the various substrates of DPP4 are a potential explanation. Finally, the play of chance cannot be excluded in this very large trial.

Whatever the underlying explanation, the results of this large outcome trial in type 2 diabetes mellitus rule out a class effect of DPP4 inhibitors on heart failure events and are therefore reassuring regarding the safety of sitagliptin in patients with pre-existing heart failure or at high risk of heart failure.

Another trial, EMPA-REG OUTCOME, tested two doses of an inhibitor of sodium-glucose co-transporter 2, empagliflozin vs. placebo in 7020 patients with type 2 diabetes at high cardiovascular risk.[5] After a median observation time of 3.1 years, the primary outcome made of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke was significantly reduced by 14% in the pooled empagliflozin group. Interestingly, hospitalizations for heart failure and the composite of hospitalization for heart failure or death from cardiovascular causes, two secondary endpoints, were also significantly reduced by 35% (*P* = 0.002) and 34% (*P* < 0.01), respectively, suggesting that this new anti-diabetic agent added to standard therapy is not only safe but also beneficial for the prevention of heart failure hospitalizations in type 2 diabetes mellitus.

Management of heart failure with preserved ejection fraction remains a clinical dilemma

The medical management of heart failure with preserved ejection fraction (HFpEF) remains challenging, and no drug

ma ACE inhibitorima i/ili beta-blokatorima. U ovoj prospektivnoj, randomiziranoj, otvorenoj studiji sudjelovalo je 1147 pacijenata.[6] Srednja vrijednost EF-a iznosila je 54 %. Tijekom medijana praćenja od 4,4 godine nije registrirana statistička razlika između dviju skupina u pojavnosti zajedničkoga primarnog ishoda (ukupna smrtnost, nesmrtonosni infarkt miokarda, nesmrtonosni moždani udar i hospitalizacija zbog pogoršanja ZS-a) (HR = 1,18; 95 % CI, 0,96 – 1,46; *P* = 0,11), dok je mnogo češće registrirano pogoršanje bubrežne funkcije. Dodatak olmesartana pacijentima koji se već liječe kombinacijom ACE inhibitora i beta-blokatora bio je povezan sa znatnim povećanjem pojavnosti primarnih ishoda (HR = 1,47; 95 % CI, 1,11 – 1,95; *P* = 0,006) ukupne smrtnosti i bubrežne disfunkcije. Ovakvi su rezultati doveli do zaključka da kombinacija liječenja ACE inhibitorima, blokatorima angiotenzinskih receptora i beta-blokatorima nije preporučljiva u HFpEF-u jer se povezuje s povećanim kardiovaskularnim rizikom i povećanim rizikom od bubrežne disfunkcije.

Tijekom 2013. godine istraživanje RELAX, koje je bilo provedeno u 216 starijih pacijenata s HFpEF-om, dokazalo je odsutnost učinka infibitora fosfodiesteraze sildenafila na maksimalnu sposobnost vježbe, udaljenost hodne pruge pri testiranju od 6 minuta, kliničkog statusa, kvalitete života, remodeliranja lijeve klijetke ili dijastoličke funkcije nakon praćenja od 24 tjedna.[7] Ovakvi su rezultati oprečni s prethodnom studijom provedenom u jednom centru koja je pokazala korisnost od praćenja na hemodinamskim varijablama mjerenima invazivnim metodama, ehokardiografskim varijablama i kvaliteti života u pacijenata s plućnom hipertenzijom povezanom s HFpEF-om.[8]

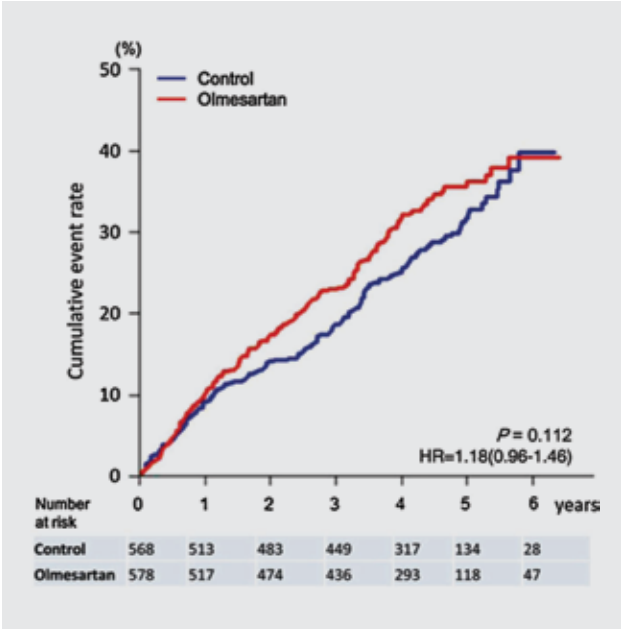

FIGURE 1. Kaplan Meier curve for the primary composite endpoint (all cause death, non fatal myocardial infarction, non fatal stroke and hospitalization for worsening heart failure) in the overall SUPPORT population.[6]

has demonstrated a clear benefit on morbidity and mortality in this population (**Figure 1**).

The SUPPORT trial examined whether an additive treatment with an angiotensin receptor blocker, olmesartan, reduces the mortality and morbidity in hypertensive patients with chronic heart failure treated with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, or both. In this prospective randomized open-label study, 1147 patients were enrolled.[6] Mean ejection fraction was 54%. During a median follow-up of 4.4 years, there was no statistical difference in the occurrence of the primary outcome made of all-cause death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for worsening heart failure between the two groups (HR = 1.18; 95% CI, 0.96–1.46; *P* = 0.11), whereas a significant increase in worsening renal function was observed. The addition of olmesartan to patients treated by the combination of ACE inhibitors and beta blockers was, however, associated with a significant increase in the occurrence of the primary endpoint (HR = 1.47; 95% CI, 1.11–1.95; *P* = 0.006) all-cause death and renal dysfunction. These findings lead to the conclusion that combination therapy of ACE inhibitors, angiotensin receptor antagonists, and beta blockers is not recommended in HFpEF since it is associated with increased cardiovascular risk and increased risk of renal dysfunction.

In 2013, the RELAX trial conducted in 216 elderly patients with HFpEF showed the absence of effect of the phosphodiesterase type 5 sildenafil on maximal exercise capacity, 6 min walking distance, clinical status, quality of life, left ventricular remodelling or diastolic function after 24 weeks of follow-up.[7] These results were in contrast with a previous single centre study that showed benefit on invasively measured haemodynamics, echocardiographic variables, and quality of life in patients with pulmonary hypertension related to HFpEF.[8]

Another just recently published single centre study by Hoendermis *et al.* published in the *European Heart Journal*, however, casts further doubt on the use of sildenafil in HFpEF patients with associated pulmonary hypertension.[9] Fifty-two patients with HFpEF and predominantly isolated post-capillary pulmonary hypertension were randomized to sildenafil or placebo. After 24 weeks, sildenafil did not reduce pulmonary artery pressures and did not improve other invasive haemodynamic or clinical parameters, thus confirming the findings of the aforementioned RELAX study that HFpEF patients with associated pulmonary hypertension do not benefit from treatment with this drug.

The current paradigm of HFpEF is that an abnormal nitric oxide bioavailability results in decreased cyclic guanylate monophosphate (cGMP) in the myocytes. One potential explanation of the lack of benefit from sildenafil is therefore that the defect is more a decrease in the production of cGMP than a problem of increased degradation that is inhibited by PDE5 inhibitors such as sildenafil. It will therefore be interesting to see the results of studies using a soluble guanylate cyclase (sGC) stimulator, such as riociguat, which is currently under evaluation. The results of the SOCRATES-REDUCED study, however, highlight the challenges in moving the concept of modulating sGC and thereby addressing the relative cGMP

Međutim, još jedna, nedavna studija objavljena u časopisu *European Heart Journal*, s rezultatima iz jednog centra čiji su autori Hoendermis *i sur.* još više stavlja pod sumnju primjenu sildenafila u pacijenata s HFpEF-om i plućnom hipertenzijom.[9] Pedeset dva pacijenta s HFpEF-om i pretežno izoliranom postkapilarnom plućnom hipertenzijom bila su randomizirana u skupine na sildenafil ili placebo. Nakon 24 tjedna sildenafil nije smanjio tlak u plućnoj arteriji niti poboljšao druge invazivne hemodinamiske ili kliničke varijable. Tako su potvrđeni rezultati prethodno spomenute studije RELAX da pacijenti s HFpEF-om i plućnom hipertenzijom nemaju dobrobiti od primjene ovog lijeka.

Trenutačna paradigma HFpEF-a jest da abnormalna biodostupnost dušikova oksida dovodi do smanjenja cikličnog guanilatmonofosfata (cGMP) u miocitima. Jedno moguće objašnjene nedostatka učinka sildenafila jest da je defekt više rezultat smanjenosti proizvodnje cGMP-a nego problem povećane degradacije koja je spriječena PDE5 inhibitorima poput sildenafila. Stoga će biti zanimljivo vidjeti rezultate studije koja se koristi stimulatorom topljive guantilatcilaze (sGC) poput riociguata, koji se trenutačno istražuje. Rezultati SOCRATES-REDUCED studije, međutim, naglašavaju izazove u unapređivanju koncepta modulirajućeg sGC-a i bavljenja relativnim nedostatkom cGMP-a.[10] U SOCRATES-REDUCED, kliničkoj studiji faze II, istražuje se doza peroralnog sGC stimulatora vericiguata u pacijenata sa smanjenom EF i pogoršanjem kronične faze ZS-a. Nije postignut primarni ishod – smanjenje vrijednosti NT-proBNP-a nakon 12 tjedana kad su analizirane sve doze, no lijek je bio dobro podnošljiv. Dodatna analiza upućivala je na učinkovitost i sigurnost u skupini s 10 mg, no potrebne su daljnje studije da bi se odredila potencijalna uloga ove skupine lijekova za pacijente s pogoršanjem kronične faze ZS-a.

Trenutačna paradigma koja tvrdi da povećanje biodostupnosti dušikova oksida može pružiti značajnu kliničku korist dovedena je u pitanje nedavno objavljenim rezultatima multicentrične, dvostruko slijepe, placebom kontrolirane studije NEAT-HFpEF.[11]

U toj studiji, koju je financirao *National Heart, Lung, and Blood Institute*, 110 pacijenata sa ZS-om i održanom EF bilo je nasumično randomizirano na režim 6-tjednog povećanja doze izosorbidmononitrata (od 30 do 60 mg do 120 mg jednom na dan) ili placebo, s naknadnim križanjem u drugu grupu na 6 tjedana. Zanimljivo je da je svaki testirani pacijent s HFpEF-om s dozom nitrata imao smanjenu razinu aktivnosti i nije imao bolju kvalitetu života ili submaksimalnu sposobnost podnošenja napora u usporedbi s pacijentima na placebu. Značajno je da nije registrirana interakcija među podgrupama, uključujući grupiranje po dobi, spolu, etiologiji ZS-a, ili vrijednostima natriuretskog peptida ili arterijskoga tlaka.

Zanimljivo je pitanje bi li drugi donori dušikova oksida, osim izosorbidmononitrata, poput anorganskog nitrita ili nitrata (za koje se pokazalo da povećavaju biodostupnost dušikova oksida tijekom vježbanja) imali bolje rezultate pod uvjetima ove studije. Bez obzira na to, donekle neintuitivni rezultati studije NEAT-HFpEF još jednom naglašavaju jasne patofiziološke razlike između ZS-a s održanom u odnosu prema ZS-u sa smanjenom EF (HFrEF). Iako dugodjelujući nitrati podeficit forward.[10] In SOCRATES-REDUCED, a phase 2 dose-finding study in patients with heart failure with reduced ejection fraction and worsening chronic HF, the oral sGC stimulator vericiguat did not meet its primary endpoint of reducing N-terminal pro-B-type natriuretic peptide (NT-proBNP) at 12 weeks when all doses were combined, but was well tolerated. While subgroup analysis did suggest efficacy and safety in its 10 mg subgroup, further studies are needed to determine the potential role of this class of drugs for patients with worsening chronic HF.

The current paradigm that increasing nitric oxide bioavailability may provide meaningful net clinical benefit was further questioned by the just recently published results of the multicentre, double-blind, placebo-controlled Nitrate's Effect on Activity, Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT-HFpEF) trial.[11]

In this National Heart, Lung, and Blood Institute-sponsored trial, 110 patients with heart failure and preserved ejection fraction were randomly assigned to a 6-week dose-escalation regimen of isosorbide mononitrate (from 30 to 60 mg to 120 mg once daily) or placebo, with subsequent crossover to the other group for 6 weeks. Intriguingly, at every tested nitrate dose patients with HFpEF had lower levels of activity and did not have better quality of life or submaximal exercise capacity than patients taking placebo. Of note, no interaction between the subgroups, including by age, sex, heart failure aetiology, natriuretic peptide levels, or blood pressure, was observed.

It is intriguing to speculate whether other Nitric Oxyde donors than isosorbide mononitrate, such as inorganic nitrite or nitrate (which have been shown to increase nitric oxide bioavailability during exercise), might have yielded more beneficial results under the conditions of the study. This notwithstanding, the somewhat counterintuitive findings of NEAT-HFpEF once again highlight the distinct pathophysiologic differences between HFpEF vs. heart failure with reduced ejection fraction (HFrEF). Indeed, since long-acting nitrates improve symptoms in HFrEF, the results of NEAT-HFpEF therefore suggest that the potential haemodynamic benefits of nitrates are less likely to come into play under the conditions of increased ventricular systolic and vascular stiffness, autonomic dysfunction, chronotropic incompetence, and altered baroreflex sensitivity as they are common in in patients with HFpEF.

Angioedema and angiotensin-converting enzyme inhibitors

Angioedema is a rare but potentially life-threatening side effects of ACE inhibitors and there is no approved treatment. It is generally related to the inhibition of the degradation of bradykinin, therefore increasing the activity of this peptide. A phase 2 study compared the effects of subcutaneous icatiband, a selective bradykinin B2 receptor antagonist to intravenous prednisolone plus an antihistaminic agent, clemastine, in 27 patients who had ACE-induced angioedema of the upper aerodigestive tract.[12] Icatiband induced a complete resolution of symptoms in 8 h on average compared with 27 h with standard therapy.

boljšavaju simptome HFrEF-a, rezultati studije NEAT-HFpEF pokazuju da je moguća hemodinamska korist od nitrata manje vjerojatna pod uvjetima povećane ventrikulske sistoličke i vaskularne krutosti, autonomne disfunkcije, kronotropne inkompetencije i promijenjene osjetljivosti barorefleksa, što je sve prisutno u pacijenata s HFpEF-om.

Angioedem i inhibitori angiotenzinkonvertirajućeg enzima

Angioedem je rijetka, ali potencijalno za život opasna nuspojava ACE inhibitora za koju ne postoji odobreno liječenje. Najčešće je povezan s inhibicijom degradacije bradikinina te povećava aktivnost tog peptida. Klinička studija faze II uspoređivala je učinak potkožno primijenjenog icatibanda, selektivnog antagonista bradikinin B2-receptora prema intravenskiprimjenjenom prednizolonu s klemastinom (antihistaminik) u 27 pacijenata koji su imali angioedem uzrokovan ACE-om u gornjim dijelovima dišnog i probavnog trakta.[12] Icatiband je doveo do potpuna nestanka simptoma u prosjeku u roku od 8 sati u odnosu prema 27 sati kod standardno primijenjenih lijekova.

Spomenuti rezultati upućuju na to da uporaba antagonista bradikininskih receptora omogućuje potpunu regresiju angioedema uzrokovana ACE inhibitorima, brže od standardno primijenjenih lijekova.

Konzumacija alkohola i rizik od zatajivanja srca

Prekomjerna konzumacija alkohola povezana je s disfunkcijom srca i eventualnim razvojem alkoholne kardiomiopatije (**slika 2**). Međutim, povezanost između umjerene konzumacije alkohola i ZS-a je kontroverzna. U 14 629 pacijenata bez

These results suggest that the use of a bradykinin receptor antagonist allows complete resolution of ACE inhibitors induced angioedema faster than with the standard therapy.

Alcohol consumption and risk of heart failure

Heavy alcohol consumption is associated with cardiac dysfunction and eventual alcoholic cardiomyopathy (**Figure 2**). However, the relationship between moderate alcohol intake and risk of heart failure is controversial. Self-reported alcohol consumption was assessed in 14 629 participants of the Atherosclerosis Risk in Communities (ARIC) study without prevalent heart failure at baseline.[13] During an average follow-up of 24 years, incident heart failure occurred in 1271 men and 1237 women. Men consuming up to 7 drinks a week (one drink = 14 g of alcohol) had a reduced risk of heart failure relative to abstainers (HR = 0.80; 95% CI, 0.68–0.94; *P* = 0.006). This '*protective*' effect was less robust in women (HR = 0.84; 95% CI, 0.71–1.00; *P* = 0.05). In the heavy drinking categories, the risk of heart failure was not different from abstainers either in women or in men. These results suggest therefore that modest alcohol consumption may be associated with a lower risk of heart failure.

Gene therapy in chronic heart failure: disappointment

Cardiac regeneration using gene transfer in the myocardium is a novel approach to the treatment of heart failure. Abnormal calcium cycling in the cardiomyocytes is a hall mark of moderate to severe heart failure, and one key element is deficient expression and activity of sarcoplasmic reticulum Ca^{2+}ATPase type 2a (SERCA2a), the molecule that pumps

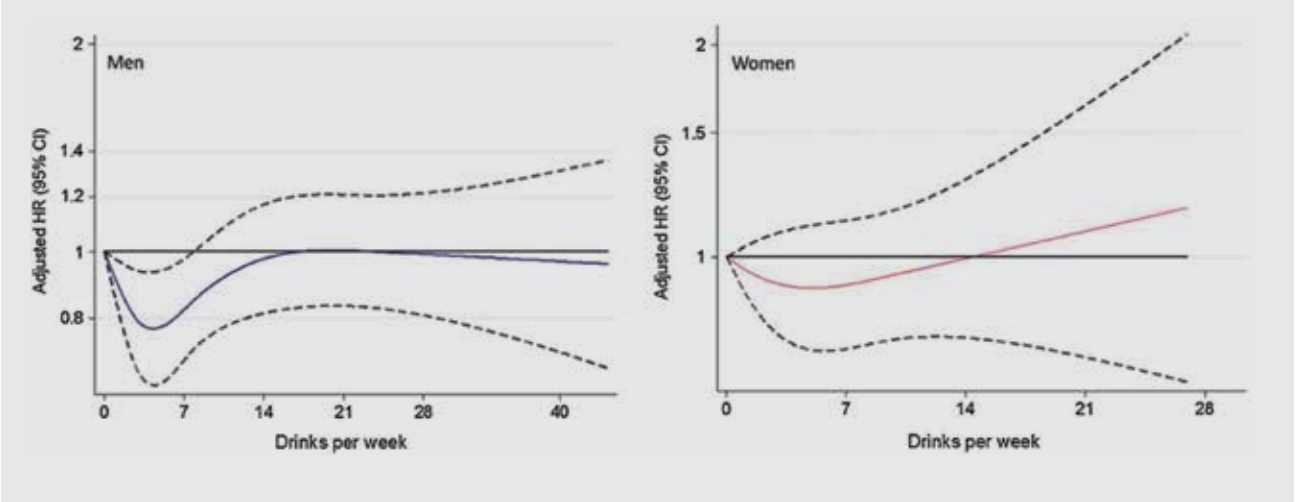

FIGURE 2. Relative risk of incident heart failure as a function of alcohol intake at baseline by sex. The 95% confidence intervals are indicated by the dash lines. Models are adjusted for age, diabetes, hypertension, coronary artery disease, body mass index, total cholesterol physical activity, education level, smoking status and incident myocardial infarction as time-varying covariate.[13]

ZS-a na početku istraživanja, procijenjena je subjektivna razina konzumacije alkohola u studiji *Atherosclerosis Riskin Communities*.[13] Tijekom prosječnoga praćenja od 24 godine, ZS je nastupio u 1271 muškarca i 1237 žena. Muškarci koji su konzumirali do 7 pića tjedno (jedno piće = 14 g alkohola) imali su smanjen rizik od ZS-a u usporedbi s onimae koji su se suzdržavali od alkohola (HR = 0,80; 95 % CI, 0,68 – 0,94; *P* = 0,006). Ovaj "zaštitni" učinak bio je manje izražen u žena (HR = 0,84; 95% CI, 0,71–1.00; *P* = 0,05). U kategoriji prekomjerne konzumacije alkohola u osoba obaju spolova rizik od ZS-a nije bio različit od onog u skupini koja nije uzimala alkoholna pića. Ovi rezultati upućuju na to da se umjerena konzumacija alkohola može povezati sa smanjenim rizikom od ZS-a.

Genska terapija pri kroničnom zatajivanju srca: razočaranje

Kardiološka regeneracija putem genskog transfera u miokard novi je pristup u liječenju ZS-a. Abnormalno kolanje kalcija u kardiomiocitima obilježje je umjerenog do ozbiljnog ZS-a, a jedan od ključnih elemenata jest nedovoljna ekspresija ili aktivnost sarkoplazmičnog retikula Ca^{2+}ATPase tipa 2a (SERCA2a), molekule koja crpi kalcij iz citosola do unutarstaničnih spremnika, tj. do sarkoplazmatskog retikula. Pretkliničke su studije pokazale da povećana ekspresija SERCA2a u kardiomiocitima normalizira kolanje kalcija te da genski transfer SERCA2a kod velikih životinjskih modela može preokrenuti disfunkciju srca. Studija CUPID 2 bila je uključila 250 bolesnika s ozbiljnim stupnjem ZS-a koji su intrakoronarno primili ili transgen (123) ili placebo (127).[14] Primarni je ishod bilo vrijeme do hospitalizacije zbog ponovljenog ZS-a i ambulantno registriranog pogoršanja ZS-a uz postojanje smrtnih događaja, uključujući ukupnu smrtnosti ili transplataciju srca. Nije bilo utvrđene razlike između obiju skupina ni u primarnim ishodima (HR = 0,93; 95% CI, 0,53–1,65; *P* = 0,81), a ni u bilo kojim sekundarnim ishodima. Nije bilo sigurnosnih problema tijekom studije. Ovi razočaravajući rezultati nemaju jasnog objašnjenja te su oprečni rezultatima prethodne manje studije (CUPID), koja je pokazala da je intrakoronarna injekcija SERCA2a transgena povezana s povoljnim, o dozi ovisnim učincima na funkciju klijetki i na razine biomarkera nakon 6 i 12 mjeseci te da su se učinci poboljšali nakon tri godine u pacijenata liječenih visokim dozama. Moguća objašnjenja neuspjeha uključuju dozu transgena, način injekcije, trajnost učinaka, vrstu vektora (ovdje endovirus) i promotera (citomegalovirus) ili metu. Postoji nada da ovakvi negativni rezultati neće zaustaviti istraživanja u ovom području te da će biti testirani drukčiji pristupi, uključujući više kardiološki specifičnih promotera, vrsta injekcije ili vektora da bi se bolje procijenila uloga genskog transfera u kardiološkoj regeneraciji.

Liječenje Chagasove kardiomiopatije benznidazolom

Chagasova je bolest česta parazitarna bolest u Južnoj Americi koja je odgovorna za najčešći oblik neishemijske kardiomiopatije u tom području. Chagasova se kardiomiopatija razvija u 25 % pacijenata zaraženih sa *Trypanosoma cruzi* nakon 20 – calcium from the cytosol to the intracellular stores, i.e. the sarcoplasmic reticulum. Preclinical studies have shown that the increased expression of SERCA2a in cardiomyocytes normalizes calcium cycling and that SERCA2a gene transfer in large animal models can reverse cardiac dysfunction. CUPID 2 enrolled 250 patients with severe heart failure who received intracoronary either the transgene (123) or placebo (127).[14] The primary endpoint was time to recurrent heart failure-related hospitalizations and ambulatory worsening heart failure in presence of terminal events, including all-cause death or transplant. There was no difference between the active and the conventional arms for the primary endpoint (HR = 0.93; 95% CI, 0.53–1.65; *P* = 0.81) or for any of the secondary endpoints. No safety issue was raised during the trial. These disappointing results have no clear explanation and are in particular in contradiction with a previous smaller trial (CUPID), which suggested that intracoronary injection of SERCA2a transgene was associated with a dose-dependent beneficial effect on ventricular function, patient well-being, and biomarkers at 6 and 12 months and that outcomes were improved at 3 years in the patients treated with the high dose. Potential explanations for failure include dose of the transgene, mode of injection, durability of the effect, type of vector (here an adenovirus) and promoter (cytomegalovirus), or the target. It is hoped that these negative results will not freeze research in this area and that different approaches including more cardio specific promoters, mode of injection, or vectors will be tested to better assess the potential role of gene transfer for cardiac regeneration.

Treatment of Chagas' cardiomyopathy by benznidazole

Chagas'disease is a common parasitic disease in Latin America and is responsible for the most common form of non-ischaemic cardiomyopathy in this area. Chagas'cardiomyopathy develops in 25% of patients infected by *Trypanosoma cruzi* 20–30 years after the acute infection. The role of trypanocidal therapy at the stage of Chagas'cardiomyopathy is unproven .The Benznidazole Evaluation for Interrupting Trypanosomiasis (BENEFIT) trial evaluated the effects on outcomes of oral benznidazole, a trypanocidal agent vs. placebo in 2854 patients who had evidence of Chagas'cardiomyopathy.[15] The drug was administered for 40–80 days and patients were followed for a mean of 5.4 years. The primary outcome was time to death, resuscitated ventricular tachycardia, insertion of a pacemaker or implantable cardioverter-defibrillator, cardiac transplantation, new heart failure, stroke, or other thromboembolic event. Although trypanocidal therapy with benznidazole significantly reduced serum parasite detection by polymerase chain reaction, there was no significant effect on the primary outcome (HR = 0.93; 95% CI, 0.81–1.07; *P* = 0.31). Potential explanations for these negative results include genetic variations of *T. cruzi*, insufficient period of observation, and late treatment at a stage of advanced cardiac disease.

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30 godina od akutne infekcije. Uloga tripanocidalnog liječenja u stupnju Chagasove kardiomiopatije nije dokazana. Studija *Benznidazole Evaluation for Interrupting Trypanosomiasis* procjenjivala je učinke oralno primijenjenog benznidazola (tripanocidalnog lijeka) u odnosu prema placebu na ishode u 2854 pacijenta kod kojih je bilo dokaza Chagasove kardiomiopatije.[15] Lijek je propisan tijekom 40 – 80 dana, a pacijenti su bili praćeni prosječno 5,4 godine. Primarni su ishodi bili vrijeme do smrti, ventrikulska tahikardija koja je zahtijevala reanimaciju, ugrađivanje elektrostimulatora ili implantibilnog kardioverterskog defibrilatora, transplatiranje srca, novonastalo ZS, moždani udar ili drugi tromboembolijski događaj. Iako je tripanocidno liječenje benznidazolom znatno smanjilo detekciju seruma parazita putem lančane reakcije polimerazom, nije bilo značajnog učinka na primarne ishode (HR = 0,93; 95 % CI, 0,81 – 1,07; *P* = 0,31). Moguće objašnjenje ovih negativnih rezultata uključuje genske varijacije *T. cruzi*, nedovoljno dugo razdoblje praćenja i kasno liječenje u stupnju uznapredovale srčane bolesti.

Conflict of interest: *M.K. reports board membership with Novartis, BMS, AstraZeneca, and Menarini; consultancy fees from Servier and Amgen; and fees from Servier, Sanofi, AstraZeneca, BMS, MSD, Menarini, and Novartis. F.R. reports grants from SJM and fees from Servier, Zoll, AstraZeneca, and HeartWare.*

LITERATURE

1. Cowie MR, Woehrle H, Wegscheider K, Angermann C, D'Ortho MP, Erdmann E, et al. Adaptive servo-ventilation for central sleep apnea in systolic heart failure. N Engl J Med. 2015;373(12):1095-105. **DOI:** http://dx.doi.org/10.1056/NEJMoa1506459
2. Scirica BM, Bhatt DL, Braunwald E, Steg G, Davison J, Hirshberg B, et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317-26. **DOI:** http://dx.doi.org/10.1056/NEJMoa1307684
3. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327-35. **DOI:** http://dx.doi.org/10.1056/NEJMoa1305889
4. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al; TECOS Study Group. Effect of Sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015 Jul 16;373(3):232-42. **DOI:** http://dx.doi.org/10.1056/NEJMoa1501352
5. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015 Nov 26;373(22):2117-28. **DOI:** http://dx.doi.org/10.1056/NEJMoa1504720
6. Sakata Y, Shiba N, Takahashi J, Miyata S, Nochioka K, Miura M, et al; SUPPORT Trial Investigators; SUPPORT Trial Investigators. Clinical impacts of additive use of olmesartan in hypertensive patients with chronic heart failure: the supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan (SUPPORT) trial. Eur Heart J. 2015;36(15):915-23. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehu504
7. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, et al; RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. JAMA. 2013;309(12):1268-77. **DOI:** http://dx.doi.org/10.1001/jama.2013.2024
8. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. Circulation. 2011;124(2):164-74. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.110.983866
9. Hoendermis ES, Liu LC, Hummel YM, van der Meer P, de Boer RA, Berger RM, et al. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. Eur Heart J. 2015;36(38):2565-73. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehv336
10. Gheorghiade M, Greene SJ, Butler J, Filippatos G, Lam CSP, Maggioni AP, et al; SOCRATES-REDUCED Investigators and Coordinators. Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: the SOCRATES-REDUCED randomized trial. JAMA 2015;314:2251-2262. JAMA. 2015;314(21):2251-62. **DOI:** http://dx.doi.org/10.1001/jama.2015.15734
11. Redfield MM, Anstrom KJ, Levine JA, Koepp GA, Borlaug BA, Chen HH, et al; NHLBI Heart Failure Clinical Research Network. Isosorbide mononitrate in heart failure with preserved ejection fraction. N Engl J Med. 2015;373(24):2314-24. **DOI:** http://dx.doi.org/10.1056/NEJMoa1510774
12. Baş M, Greve J, Stelter K, Havel M, Strassen U, Rotter N, et al. A randomized trial of icatibant in ACE-inhibitor-induced angioedema. N Engl J Med. 2015;372(5):418-25. **DOI:** http://dx.doi.org/10.1056/NEJMoa1312524
13. Gonçalves A, Claggett B, Jhund PS, Rosamond W, Deswal A, Aguilar D, et al. Alcohol consumption and risk of heart failure: the Atherosclerosis Risk in Communities Study. Eur Heart J. 2015 Apr 14;36(15):939-45. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehu514
14. Greenberg B, Butler J, Felker GM, Ponikowski P, Voors AA, Desai AS, et al. Calcium up-regulation by percutaneous administration of gene therapy in cardiac disease phase 2b (CUPID 2): a randomised, multinational, double-blind, placebo-controlled trial. Lancet. 2016;387(10024):1178-86. **DOI:** http://dx.doi.org/10.1016/S0140-6736(16)00082-9
15. Morillo CA, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi A Jr, Rosas F, et al; BENEFIT Investigators. Randomized trial of benznidazole for chronic Chagas' cardiomyopathy. N Engl J Med. 2015;373(14):1295-306. **DOI:** http://dx.doi.org/10.1056/NEJMoa1507574