Pregledni članak Review article

Almanah 2011. godine: srčano zatajivanje.

Časopisi nacionalnih društava predstavljaju odabrana istraživanja koja predstavljaju napredak u kliničkoj kardiologiji

Almanac 2011: heart failure.

The national society journals present selected research that has driven recent advances in clinical cardiology

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Pružanje skrbi

NICE, revizija i briga oko zatajivanja srca

Nacionalna revizija[1] zatajivanja srca (ZS) koja se provodi u Engleskoj i Walesu nastavlja s rastom te pruža važne podatke za planiranje usluga koje se pružaju u svezi sa ZS. Prvo formalno izvješće se odnosi na više od 6.000 bolesnika koji su bili između prvih 10 zaprimljenih s primarnom dijagnozom ZS svakog mjeseca u jednu od 86 bolnica, što je predstavljalo izvor podataka za razdoblje od 2008. do 2009. godine. Većina je imala sistoličku disfunkciju lijeve klijetke (LK), ali je ehokardiografski nalaz bio dostupan kod samo 75% bolesnika. Bolnička smrtnost iznosila je 12%, a od preživjelih pri otpustu iz bolnice 80% ih je bilo liječeno ACE inhibitorom (ili blokatorom receptora angiotenzina (ARB)), 50% beta-blokatorom te 30% antagonistom aldosterona.

Revizija 21.000 bolesnika hospitaliziranih radi ZS u razdoblju 2009.—2010. također je dostupna.[2] Bolnička smrtnost se blago smanjila na 10,5%, ali nije bilo dramatične promjene u učestalosti propisivanja lijekova. Neke podskupine bolesnika bile su aktivnije liječene (muškarci od 55 do 64 godine, stopa propisivanja beta-blokatora >70%), a kod drugih je aktivno liječenje bilo puno manje vjerojatno (žene starije od >85, stopa propisivanja beta-blokatora 40%). Antagonisti aldosterona propisivali su se još uvijek kod manje od polovice bolesnika.

Dvije karakteristike se izdvajaju iz podataka obje revizije. Prvo, učestalost propisivanja jako varira, s dobi — stariji bolesnici i žene imaju manju mogućnost za liječenje — te s mjestom prijma — bolesnici primljeni na odjel kardiologije imaju puno veću mogućnost za aktivno liječenje. Drugo, farmakološko liječenje i preživljenje bili su bolji kod bolesnika liječenih od kardiologa. Iako je manjina bolesnika koja se primila radi ZS bila zbrinuta od strane kardiologa, učinak na preživljenje postojao je i nakon korekcije za dob i spol (i drugih čimbenika).

Nedovoljno liječenje starijih bolesnika sa ZS predstavlja naročit problem u vrijeme kada pacijenti stariji od 80 godina predstavljaju sve veći udio pri prijmu zbog ZS.[3] Liječenje starijih bolesnika je otežano zbog njihovih povezanih kormobiditeta i uzimanja više lijekova, kao i zbog njihovog sustavnog isključivanja iz kliničkih istraživanja te stoga nedostupnosti dokaza potrebnih liječnicima za donošenje odluke o zbrinjavanju.[4] Isključivanje starijih osoba od strane organizatora istraživanja ne pokazuju trend

Provision of care

NICE, audit and heart failure care

The national heart failure (HF) audit[1] in England and Wales continues to grow and provides vital data for planning HF services. The first formal report relates to over 6000 patients who were the first 10 patients admitted with a primary diagnosis of HF each month to one of 86 hospitals contributing data in 2008 — 09. Most had left ventricular (LV) systolic dysfunction, but an echocardiogram result was available in only 75%. In-patient mortality was 12% and in survivors, 80% were receiving an ACE inhibitor (or angiotensin receptor blocker (ARB)), 50% a β blocker and 30% an aldosterone antagonist at discharge.

The audit for 21,000 patients hospitalised with HF in 2009-10 is also available.[2] In-hospital mortality had fallen slightly to 10.5%, but there was no dramatic change in drug prescription rates. Some subsets of patients were particularly likely to be actively treated (men aged 55-64, β blocker prescription rate >70%), and others much less likely (women aged >85, β blocker prescription rate 40%). Aldosterone antagonists were still prescribed for less than half the population.

Two striking features stand out from the data from both audits. First, prescription rates vary greatly, with age-older patients and women being less likely to be treated-and with admission ward-patients admitted to cardiology wards being much more likely to receive active treatment. Second, pharmacological treatment was better for patients admitted under cardiologists, and so was survival. Although a minority of patients admitted with HF are managed by cardiologists, the survival benefit persists after correction for age and sex (and other confounders).

The undertreatment of elderly patients with HF is a particular cause for concern at a time when patients aged >80 represent an increasing proportion of admissions for HF.[3] Treatment of older patients is hampered by their associated comorbidities and polypharmacy and also by their systematic exclusion from clinical trials, depriving doctors of the evidence base they need to guide management decisions.[4] Exclusion of the elderly by trial organisers shows no signs of going away: among 251 trials recruiting patients in

poboljšanja: između 251 bolesnika uključenih u istraživanja u prosincu 2008. godine, više od 25% je bilo gornje starosne granice za uključenje, a više od 80% isključenih bolesnika imalo je komorbiditet.[4]

Nacionalni institut zdravlja i kliničke izvrsnosti (NICE) objavio je najaktualnije smjernice za zbrinjavanje ZS.[5,6] Ima dosta komentara o značaju mjerenja vrijednosti natriuretskih peptida kao polazne točke ZS te također oko preporuke da bi skrb specijaliste za ZS trebala biti standard. To je točno kod procjene i dijagnoze (bolesnik za kojeg se sumnja da je imao ZS vezano za prethodni infarkt miokarda ili s vrlo visokom razinom natriuretskog peptida bi trebao primiti "... specijalistička procjena unutar dva tjedna") te tijekom prijma u bolnicu ("kada se bolesnika primi u bolnicu zbog ZS, potražiti savjet o planu zbrinjavanja od specijaliste za ZS").

Takve preporuke će nametnuti nova opterećenja. Što je 'specijalist'? NICE smatra da je "...liječnik sa subspecijalističkim interesom za ZS (često konzultant kardiolog) koji vodi stručni multidisciplinarni tim stručnjaka za ZS...", ali je malo osoba koje mogu preuzeti odgovornost. No, neovisno o tome kako se definira specijalist, bolesnici su zbrinuti bolje ukoliko se za njih brinu stručnjaci s posebnom specijalizacijom za to područje. To se vidi u novijim podacima SAD-a koji su pokazali nižu smrtnost i manju učestalost hospitalizacije za bolesnike sa ZS koje se zbrinjavaju u visokovolumnim u odnosu na centre niskog volumena.[7]

Jedan od problema za specijalistu za ZS je pristup naprednom liječenju kao što je transplantacija srca. Učestalost transplantacija u UK se smanjuje, djelomično zbog smanjene dostupnosti doniranih organa,[8] ali jednako značajna je i dostupnost eksperata za ZS.[9] Uspjeli smo reorganizirati zdravstvenu skrb kako bi omogućili primarnu angioplastiku za bolesnike s akutnim infarktom miokarda (IM) (uključujući bolesnike s IM bez elevacije ST segmenta na prilično slabim dokazima[10]). Isto bi trebalo učiniti za bolesnike sa ZS za koje će ponovno uspostavljene usluge imati dalekosežne koristi.

Telemonitoring

Značajan napredak za skrb bolesnika sa ZS predstavlja uporaba daljinskog monitoriranja temeljem kojeg se može promijeniti liječenje. Tipično se automatskim uređajima kod kuće mogu izmjeriti tjelesna težina, srčana frekvencija i ritam i arterijski tlak (AT) te podaci prenijeti u centralnu jedinicu. Rezultati koji odstupaju od normalnih vrijednosti mogu dovesti do promjene liječenja pojedinog bolesnika. Početna istraživanja govore da ovakav sustav može biti koristi, posebno ukoliko se koristi zajedno s telefonskim kontaktom.[11]

Poseban problem kod telemonitoringa je što učiniti s prikupljenim podacima. Kako se radi o velikom broju bolesnika koji potencijalno prenose znatne količine podataka dnevno, izvor koji je potreban za obradu podataka može postati ogroman. Pokušaji da se koriste automatski sustavi pokazali su se razočaravajućim: u studiji od 1.653 bolesnika koji su bili nedavno hospitalizirani zbog ZS koristio se telemonitoring s interaktivnim sustavom glasovnog odgovora čime su se dnevno prikupljali podaci o simptomima i težini. *Chaudry i sur.* utvrdili su da primjena ovog sustava nema utjecaja na ponovni prijam i smrtnost unutar 6 mjeseci.[12] U drugoj studiji,[13] telemonitoring nije popravio re-

December 2008, more than 25% had an upper age limit for enrolment and more than 80% excluded patients with comorbid conditions.[4]

The National Institute for Health and Clinical Excellence (NICE) has produced updated guidelines for HF care.[5,6] While there has been a lot of comment on the importance of measuring natriuretic peptides as an entry point to HF care, NICE has also firmly recommended that care led by a specialist in HF should be the norm. This is true at assessment and diagnosis (a patient suspected of having HF associated with a previous myocardial infarct or with a very high natriuretic peptide level should receive "...specialist assessment within 2 weeks") and during admission to hospital ("when a patient is admitted to hospital because of HF, seek advice on their management plan from a specialist in HF").

Such recommendations will impose new burdens. What is a 'specialist'? NICE thinks it is "...a doctor with subspecialty interest in HF (often a consultant cardiologist) who leads a specialist multidisciplinary HF team of professionals ...", but there are few such individuals available to take up the responsibility. However a specialist is defined, there is no doubt that patients with HF fare better when cared for by professionals with a particular interest in their condition. This is reflected in recent US data that have shown lower mortality and readmissions for patients with HF managed in high-volume compared with low-volume centres.[7]

One of the problems for a specialist HF service is access to advanced treatments such as heart transplantation. Transplantation in the UK is falling, partly owing to a fall in the availability of donor organs,[8] but just as important is access to expert HF care.[9] We have managed to reconfigure health services to provide primary angioplasty for patients with acute myocardial infarction (MI) (including for patients with non-ST elevation MI on rather flimsy evidence[10]). We should do so for patients with HF, for whom reconfigured services will have a more far-reaching benefit.

Telemonitoring

An exciting possible advance in patient care is the use of remote monitoring to guide changes in treatment. Typically, automated devices in the home can measure weight, pulse rate and heart rhythm and blood pressure (BP) and transmit the data to a centre. Abnormal results then trigger patient contact with possible change in treatment. Initial trials have suggested that there may be a benefit from such systems, particularly when coupled with telephone contact.[11]

A particular problem with telemonitoring is what to do with the data. With a large number of patients potentially transmitting quantities of data daily, the resource required to deal with the data might become impossibly large. Attempts to use automated systems have proved disappointing: in a study of 1,653 patients who had recently been hospitalised for HF, which used telemonitoring with an interactive voice-response system collecting daily information about symptoms and weight, *Chaudry et al* found no impact on re-admissions and mortality at 6 months.[12] In another recent study,[13] remote monitoring did not improve outcomes among 710 patients randomised to remote mo-

zultate kod 710 bolesnika koji su bili randomizirani na daljinsko praćenje koristeći sustav koji je prenosio EKG, AT i težinu te je uključivao sustav hitnih poziva.

Važno je zapamtiti da telemomitoring sam po sebi ne spašava živote ili smanjuje učestalost hospitalizacija, ali bi se radnjama koje se poduzimaju kao odgovor na to praćenje spomenuto moglo postići. Razlog zašto su novija istraživanja neutralna može biti da je "uobičajena skrb" u ovim studijama napredovala do mjere kada praćenje od kuće može imati malu dodatnu dobrobit pa telemonitoring može pomoći samo kod visokorizičnih pacijenata. Moguće je da su varijable koje su mjerene prešture da bi bile od koristi za promjenu liječenja.

Drugi pristup daljinskom praćenju je korištenje uređaja za implantaciju radi invazivnog mjerenja hemodinamskih primjena. Chronicle uređaj omogućava stalno praćenje plućnog arterijskog tlaka i početno istraživanje (COMPASS) je sugeriralo da je isti mogao biti od koristi.[14] Tehnika koja više obećava je primjena manjih uređaja izravno ugrađenih u plućnu arteriju i komuniciranje bežičnim akustičnim uređajem.[15] U istraživanju CHAMPION,[16] 550 bolesnika bilo je randomizirano na primjenu CardioMEMS uređaj ili primaju uobičajenu skrb. Uređaj se koristio za mjerenje tlaka plućne arterije jednom dnevno: on nema interni izvor napajanja, nego koristi vanjsku korištenu radiofrekvencijsku energiju. Njegova uporaba je bilo povezana s 30% smanjenjem primarnog ishoda hospitalizacije zbog ZS unutar 6 mjeseci. Naravno da uređaj sam po sebi nije mogao poboljšati rezultat, nego promjene u liječenju koje slijede iz očitanja nalaza. Primjerice u studijama COMPASS[14] i CHAMPION,[16] bolesnici s uređajem su liječeni višim dozama lijekova za ZS.

Konačna faza u razvoju daljinskog praćenje bi mogla za rezultat imati daljnje poboljšanje za bolesnike. Uređaji se mogu koristiti za prijenos podataka samom bolesniku koji tada može koristiti podatke za uvođenje dnevnih promjena u svojem liječenju. U studiji HOMEOSTASIS, 40 bolesnika s teškim stupnjem ZS imalo je ugrađen uređaj za mjerenje tlaka u lijevom atriju. Temeljem rezultata mjerenja izvršena je i promjena liječenja koristeći programirani ručni modul za savjetovanje bolesnika.[17] Nemoguće je donijeti konačne zaključke iz tako male opservacijske studije, ali se liječenje diureticima smanjilo kao rezultat intervencije, a primjena beta-blokatora i ACE inhibitora/ARB povećala. Istovremeno se prosječan tlak u lijevom atriju smanjio i činilo se da se broj kliničkih događaja smanjio.

Invazivno praćenje rezultiralo je povećanjem propisivanja farmakološkog liječenja za ZS čime se potencira još jedno pitanje koje nas opterećuje: iako imamo rezultate kliničkih istraživanja koja nas vode prema "ciljnim dozama", primjerice beta-blokatora i ACE inhibitora, kako bi trebali znati koje su doze dovoljne? Jedan od mogućih savjeta je primjena natriuretskih peptida: možda bi se liječenje trebalo nastaviti sve dok se ne normalizira njihova razina. Neke studije s malim brojem pacijenata su nas usmjerile u tom smjeru, dok druge nisu: ali u meta-analizi postoje dokazi o pristranosti objave.[18] Novije istraživanje s pacijentima iz jednog centra pri čemu je obuhvaćeno 364 bolesnika sa ZS je pokazalo da liječenje vođeno vrijednostima NT-proBNP bilo povezano sa jednogodišnjim mortalitetom jednako liječenju vođenom kliničkim rezultatom.[19] Nalaz daje određenu težinu argumentu protiv liječenja

nitoring using a system that transmitted ECG, BP and weight and included a home emergency call system.

It is important to remember that telemonitoring itself does not save lives or admissions, but that actions taken in response to monitoring might do so. The reason recent trials have been neutral may be that 'usual care' in these studies has progressed to the point at which home monitoring can have little additional beneficial effect and it may be that remote monitoring is only likely to be helpful in people at particularly high risk. It may be, too, that the variables measured are simply too crude to be helpful guides to changing treatment.

Another approach to remote monitoring is to use implantable devices to measure haemodynamic changes invasively. The Chronicle device allows pulmonary artery pressure to be measured continuously and an early trial (COMPASS) suggested that it might be helpful.[14] A more promising technique, perhaps, is the use of smaller devices implanted directly into the pulmonary artery and communicating using acoustic wireless communication.[15] In the CHAMPION trial,[16] 550 patients were randomised to have a CardioMEMS device or usual care. The device was used to measure pulmonary artery pressure once a day: it has no internal power source, but uses externally applied radiofrequency energy. Its use was associated with a 30% reduction in the primary efficacy end point of hospitalisation for HF at 6 months. It is not, of course, the devices that improve outcome, but the changes in treatment that follow from device readings. In COMPASS[14] and CHAMPION,[16] for example, patients with the device were receiving higher doses of medication to treat HF.

The final stage in the evolution of remote monitoring is likely to be to further empowerment of the patient. The devices can be used to transmit data to the person most concerned with the disease-the patient-who can then use the information to make daily changes to his or her treatment. In HOMEOSTASIS, 40 patients with severe HF were implanted with a device measuring left atrial pressure and made changes to treatment based on the readings using a preprogrammed hand-held patient advisor module.[17] It is impossible to draw firm conclusions from such a small observational study, but while diuretic treatment fell as a result of the intervention, β--blocker and ACE inhibitor/ARB treatment increased. At the same time, mean left atrial pressure fell and there did seem to be a reduction in clinical events.

Invasive monitoring leads to an increase in prescription of medical treatment for HF, which highlights another nagging question: although we have clinical trial results to guide us towards 'target' doses of, for example, β blockers and ACE inhibitors, how are we to know how much is enough? One possible guide is the use of natriuretic peptides: perhaps treatment should continue to be increased until the natriuretic peptide level is normal. Some small studies point in that direction, others do not: but there is evidence of publication bias in a meta-analysis.[18] A recent single-centre trial in 364 patients with HF showed that treatment guided by N-terminal pro-brain natriuretic peptide was associated with a 1-year mortality identical to treatment guided by a clinical score.[19] The finding lends some weight to the argument against biomarker-guided treat-

vođenog biomarkerima, ali će taj problem definitivno biti razriješen velikim istraživanjem.

Epidemiologija

Zatajivanje srca s normalnom istisnom frakcijom

Zatajivanje srca s normalnom istisnom frakcijom (HeFNEF) ostaje i dalje enigma. Epidemiološki podaci sugeriraju da je ovaj oblik čest[20,21] te možda iznosi čak polovicu od svih slučajeva ZS. Međutim, istraživači pri izboru pacijenata za istraživanja često imaju poteškoće u prepoznavanju odgovarajućih bolesnika. Niti jedno kliničko istraživanje do sada nije prepoznalo uspješno liječenje za HeFNEF, a neki su skeptični o postojanju ovog pojedinačnog, dobro definiranog entiteta.[22,23] Problemi nastaju, barem djelomično, jer je otežano disanje kod starijih osoba vrlo često i jer se pojedine dijastoličke ehokardiografske promjene, za koje se smatra da utvrđuju ZS, mijenjaju starenjem.

Jedna mogućnost koja je nedovoljno istražena, jest da je HeFNEF očito stanje koje se manifestira tijekom vježbe, a ehokardiografska mjerenja tijekom vježbe mogu naglasiti dijastoličke nepravilnosti.[24] Važan rezultat iz studije u kojoj je bila učinjena ehokardiografija uz vježbu kod više od 400 bolesnika s mogućim HeFNEF[25] je bio da vrlo mali broj — moguće čak 3% pacijenata su zapravo imali ZS. *Holland i sur.*[25] su naglasili važnost mjerenja odnosa između E i E' kao indeksa tlaka punjenje lijeve klijetke, dok su drugi bili usredotočeni na puno suptilnije nepravilnosti sistole i dijastole kod bolesnika sa HeFNEF koja se pogoršavala pri naporu.[26] Tome može doprinijeti i oštećena funkcija lijeve pretklijetke tijekom vježbanja.[27]

Iako je ovo vrlo aktivno područje istraživanja, temeljni problem sa HeFNEF i glavni razlog zašto nema (dokazanog) liječenja je manjak zadovoljavajuće definicije. Uvrštavanje natriuretskih peptida u dijagnostički protokol za HeFNEF bi trebao pomoći jer njihova povišena razina ukazuje da je srce uzrok smetnji. Međutim, u prošlosti se primjenom natriuretskih peptida pretjerano dijagnosticiralo HeFNEF-a. Potencijalno značajno u ovom pogledu je novija analiza podataka o uzrocima smrti iz studije I-Preserve: kod bolesnika s HeFNEF, smrt od ZS je bila iznenađujuće rijetka, a većina je podlegla kardiovaskularnim događajima.[28]

Liječenje

Neurohormonalno upravljanje

ACE inhibitori, ARB i beta-blokatori su glavne opcije liječenja bolesnika s kroničnim ZS. ACE inhibitori ili ARB bi se trebali primjenjivati kod svih bolesnika sa sistoličkom disfunkcijom lijeve klijetke, bez obzira na stupanj simptoma te je opće stajalište da bi se trebale koristiti u najvišoj podnošljivoj dozi, ograničenoj pojavom nuspojava. Dokaz za ovaj pristup dolazi od istraživanja ATLAS,[29] u kojem su bolesnici randomizirani na više doze lizinoprila imali bolje ishode od onih liječenih nižim dozama.

Sve do studije HEAAL[30] postojalo je malo dokaza da je visoka doza ARB bolja od niske. Ukupno je 3.846 bolesnika koji nisu podnosili ACE inhibitore sa ZS i istisnom frakcijom lijeve klijetke <40% bilo randomizirano na visoku (150 mg) ili nisku dozu (50 mg) losartana dnevno. Nakon

ment but the question will only be resolved by a definitive large trial.

Epidemiology

HF with a normal ejection fraction

HF with a normal ejection fraction (HeFNEF) remains enigmatic. Epidemiology suggests that it is common,[20-21] perhaps accounting for half of the cases of HF. However, researchers recruiting patients to trials have often found it extremely difficult to identify suitable patients. No clinical trial has as yet identified any successful treatment for HeFNEF and some are sceptical of its existence as a single, well-defined entity.[22-23] Problems arise because, at least in part, breathlessness is very common in older people and because some of the diastolic echocardiographic changes thought to indicate that the heart is failing are simply consistent with ageing.

One possibility that has been under-researched is that HeFNEF is more obviously a condition appreciated during exercise, and echocardiographic measurements during exercise may highlight diastolic abnormalities.[24] An important observation from a study of echocardiography and exercise of over 400 patients with possible HeFNEF[25] was that very few— possibly as few as 3% actually had HF. *Holland and colleagues*[25] emphasised the importance of measuring the ratio between E and E' as an index of LV filling pressure, but others have concentrated on much more subtle abnormalities of both systole and diastole in patients with HeFNEF that worsen with exertion.[26] Impaired left atrial function during exercise may also contribute.[27]

While it remains a very active area of research, the cardinal problem with HeFNEF and the main reason it has no (proven) treatment is the absence of a satisfactory case definition. The incorporation of natriuretic peptides into the diagnostic pathway for HeFNEF should help as a raised level makes it more certain that the heart is the cause of any symptoms. However, natriuretic peptides may show that there has been considerable overdiagnosis of HeFNEF in the past. Potentially relevant in this respect is the recent analysis of mode of death data from I-Preserve: in patients with HeFNEF, death from HF was surprisingly rare, the majority succumbing to other cardiovascular events.[28]

Treatment

Neurohormonal manipulation

ACE inhibitors, ARBs and β blockers, are of course, the mainstays of medical treatment for patients with chronic HF. ACE inhibitors or ARBs should be given to all patients with LV systolic dysfunction, regardless of symptom class, and there is general appreciation that the highest tolerated dose should be used, side effects permitting. Evidence for this approach comes from trials such as ATLAS,[29] in which patients randomised to higher-dose lisinopril fared better than those receiving a lower dose.

There has been little evidence that a high dose of ARBs is better until the HEAAL study,[30] in which 3,846 patients with HF and LV ejection fraction <40% and who were intolerant of ACE inhibitors were randomised to receive high-dose (150 mg) or low-dose (50 mg) daily losartan. Af-

prosječnih 4.7 godina praćenja učestalost smrtnosti ili hospitalizacije zbog ZS bila je niža u skupini koja je primala visoku dozu losartana (HR=0.90, 95% CI 0.82 do 0.99; p=0.027). Čini se da titriranje do viših doza ARB donosi kliničke dobrobiti.

Sa studijama RALES[31] (spironolakton) i EPHESUS[32] (eplerenon) blokada aldosterona pokazala se značajnom, iako se sve do nedavno nije pokazala korisnom kod bolesnika s blagim stupnjem ZS. U studiji EMPHASIS-HF,[33] 2.737 bolesnika sa ZS zbog sistoličke disfunkcije u II. skupini simptoma prema *New York Heart Association* (NYHA) bilo je randomizirano na eplerenon (do 50 mg dnevno) ili placebo, uz standardno liječenje. Registrirano je 37% smanjenja rizika primarnog ishoda (kardiovaskularna smrt ili hospitalizacija zbog ZS) u skupini liječenoj eplerenonom, uz cijenu malog porasta rizika hiperkalemije. Čini se vjerojatnim da će skupine za smjernice sada preporučiti korištenje eplerenona svim bolesnicima sa ZS zbog sistoličke disfunkcije lijeve klijetke.

Problem s raširenijim korištenjem antagonista aldosterona je postojanje mogućnosti porasta rizika od hiperkalemije, koja predstavlja po život opasno stanje. Zasigurno se nakon RALES studije spironolakton češće uzimao, što je uzrokovalo značajno povećanje morbiditeta i mortaliteta od hiperkalemije.[34] Mogući pristup za sprječavanje hiperkalemije predstavlja primjena resina koji vežu kalij. U studiji PEARL-HF,[35] ispitivano je 105 bolesnika sa ZS i anamnestičkim podatkom o hiperkalemiji koja je ometala njihovo liječenje ili bolesnika s kroničnim zatajivanjem bubrega. Vezivač kalija, RLY5016, primjenjen je uz spironolakton što je dovelo do značajnog smanjenja rizika od hiperkalemije u odnosu na placebo (7,3% prema 24,5%, p=0,015); a viši je bolesnika liječeno dozom od 50 mg spironolaktona dnevno (91% prema 74%, p=0,019). Ovo predstavlja optimističan rezultat, ali nas usmjerava na očito neodgovoreno pitanje: u kojoj mjeri je korist od antagonizma aldosterona uvjetovana hiperkalemijom? Ukoliko je odgovor 'uglavnom', ili 'u cijelosti', tada od vezivača kalija nema puno koristi.

Ivabradin

Mehanizam kojim beta-blokatori uvjetuju svoje korisne učinke nije jasan, ali se dugo smatra da je povezan sa njihovom sposobnošću da snize srčanu frekvenciju.[36-37] Ivabradin smanjuje srčanu frekvenciju smanjenjem ritma pražnjenja sinusnog čvora bez nekog drugog hemodinamskog utjecaja te stoga može testirati hipotezu srčane frekvencije i osigurati novu opciju bolesnicima koji ne podnose beta-blokatore.

U studiji SHIFT,[38] 6.558 bolesnika sa ZS i niskom istisnom frakcijom koji su bili u sinusnom ritmu uz frekvenciju od najmanje 70/min bilo je randomizirano na liječenje ivabradinina ili placeba uz standarnu terapiju (uključujući beta-blokator, ako ga bolesnici podnose). Ivabradin je bio povezan s 18% smanjenja primarnog ishoda (kardiovaskularna smrt ili hospitalizacija radi pogoršanja ZS), što se uglavnom vidi po smanjenju prijma u bolnicu.

Mnogo se diskutiralo o rezultatima SHIFT istraživanja. Važno je istaći da su koristi od ivabradina bile znatno više upečatljive kod onih pacijenata s višom frekvencijom u stanju mirovanja,[38,39] te iako je oko 90% bolesnika uzimalo beta-blokator na početku, samo ih je 23% uzimalo cilj-

ter a median 4.7 years' follow-up there was a lower rate of deaths or hospitalisation for HF in the high-dose group (HR=0.90, 95% CI 0.82 to 0.99; p=0.027). Thus it does thus seem that up-titrating ARB doses confers clinical benefit.

With RALES[31] (spironolactone) and EPHESUS[32] (eplerenone), aldosterone blockade has also become important, with the proviso that aldosterone blockade has not been shown to be beneficial in patients with mild HF, at least until recently. In EMPHASIS-HF,[33] 2,737 patients with HF due to systolic dysfunction and New York Heart Association (NYHA) class II symptoms were randomised to eplerenone (up to 50 mg daily) or placebo, in addition to standard treatment. There was a 37% reduction in the risk of the primary end point (cardiovascular death or hospitalisation for HF) in the eplerenone group, at the cost of a small increase in the risk of hyperkalaemia. It seems likely that guideline groups will now recommend the use of eplerenone in all those with HF due to LV systolic dysfunction.

A problem with the more widespread use of aldosterone antagonists is that the risk of life-threatening hyperkalaemia may increase. Certainly after the RALES report, there was a rapid uptake of spironolactone usage resulting in a marked increase in morbidity and mortality from hyperkalaemia.[34] A possible approach to preventing hyperkalaemia is to use potassium-binding resins. In PEARL-HF,[35] 105 patients with HF and a history of hyperkalaemia which had interfered with medical treatment, or who had chronic kidney disease, were recruited. The potassium binder, RLY5016, was given in addition to spironolactone and led to a marked reduction in the risk of hyperkalaemia compared with placebo (7.3% vs 24.5%, p=0.015); and a higher proportion of patients reaching spironolactone 50 mg/day (91% vs 74%, p=0.019). These are encouraging data, but lead to the obvious unanswered question: to what extent is the benefit of aldosterone antagonism mediated by hyperkalaemia? If the answer is 'most', or 'all', then potassium binding may not have much to offer.

Ivabradine

The mechanism by which β blockers mediate their beneficial effects is not clear, but has long been thought to be related to their ability to reduce heart rate.[36,37] Ivabradine reduces heart rate by reducing sinus node discharge rate while having no other haemodynamic effect and might thus both test the heart rate hypothesis and provide an alternative for patients intolerant of β blockers.

In SHIFT,[38] 6,558 patients with HF and a low ejection fraction and who were in sinus rhythm with a heart rate of at least 70 beats/min were randomised to receive ivabradine or placebo in addition to usual treatment (including β blocker, where tolerated). Ivabradine was associated with an 18% reduction in the primary end point (cardiovascular death or hospital admission for worsening HF), driven mainly by a reduction in hospital admission.

The findings of SHIFT have been much discussed. It is important to point out that the benefits of ivabradine were much more striking in those with a higher resting heart rate,[38,39] and that although around 90% of patients were taking a β blocker at baseline, only 23% were taking a target

nu dozu. Samo njih 49% je koristilo ≥50% ciljne doze i 16% je primalo beta-blokator koji se nije pokazao korisnim.

Rezultati SHIFT istraživanja ukazuju da postoji uloga ivabradina kod bolesnika s kroničnim ZS, ali on nije zamjena za primjenu beta-blokatora. Postoji masa dokaza koji idu u prilog primjene beta-bloktora koji smanjuju smrtnost, kao i broj hospitalizacija. Ivabradin bi se trebao razmotriti samo kod bolesnika koji imaju frekvenciju srca u mirovanju iznad 70/min usprkos maksimalno podnošljive doze beta-blokatora (ili možda koristiti kod bolesnika koji zaista ne podnose beta-blokatore). Podaci iz kliničke prakse u pacijenata sa ZS ukazuju da je udio bolesnika koji bi mogli uzimati ovaj lijek nizak, moguće oko 5%.[40]

Željezo

Je li je manjak željeza razlog za liječenje? Anemija je vrlo uobičajena pojava kod bolesnika sa ZS,[41] ali je uobičajen i nedostatak željeza bez anemije. Najbolji način za zbrinjavanje nedostatka željeza nije jasan: liječenje oralnim preparatom željeza općenito se smatralo neučinkovitim, a intravenozno davanje željeza se smatralo teškim ili opasnim. Međutim, sada je dostupna nova generacija intravenoznih preparata željeza, što omogućava brzu i sigurnu primjenu željeza bolesnicima.

Neke preliminarne studije su navele da intravenozno zasićenje željezom može dovesti do poboljšanja fizičke sposobnosti,[42] a studija FAIR-HF je bila dizajnirana da bi se utvrdilo je li željezo korisno kod veće skupine bolesnika.[43] Ukupno je 459 bolesnika je bilo randomizirano u omjeru 2:1 za liječenje infuzijom željeza ili placebom (jednostruko slijepo testiranje). Nakon 6 mjeseci je došlo do poboljšanja u globalnoj i samostalnoj ocjeni bolesnika (50% "veliko i umjereno poboljšanje", u usporedbi sa 28% bolesnika u skupini koja je primala placebo) kao i u sekundarnom ishodu, uključujući i udaljenost za vrijeme 6-minutnog testa opterećenja hodanjem (oko 40 m povećanja u usporedbi s nikakvom promjenom u skupini koja je primala placebo). Poboljšanje je registrirano neovisno o vrijednosti početnog hemoglobina.

Rezultati se moraju pažljivo analizirati: studija FAIR-HF nije bila veliko istraživanje, nepoznavanje dodjele liječenja je bilo teško uspostaviti, a primarni ishodi su bili subjektivni u različitoj mjeri. Ipak, liječenje željezom se učinilo sigurnim i sada predstavlja opciju za bolesnike koji ostaju simptomatski usprkos liječenju. Apsolutno osnovno pitanje na koje treba odgovoriti je razina do koje bi se bolesnici sa ZS trebali dalje nastaviti obrađivati radi utvrđivanja uzroka manjka željeza, no tim pitanjem se ne bavi studija FAIR-HF.

Drugi mogući pristup u liječenju anemije kod ZS je primjena proteina koji stimuliraju eritropoezu. Meta-analiza šest randomiziranih kontroliranih istraživanja je otkrila da je liječenje bilo povezano sa značajno nižim rizikom hospitalizacije u odnosu na placebo.[44] Smrtnost je ostala nepromijenjena. Ovi rezultati su u suprotnosti sa rezultatima studija o bolestima karcinoma i bubrega, pa su naveli autore da zatraže veliko istraživanje morbiditeta i mortaliteta faze III o korekciji anemije s proteinima koji stimuliraju eritropoezu u bolesnika s kroničnim ZS.

dose, only 49% were receiving ≥50% of a target dose and 16% were receiving a β blocker not shown to be beneficial.

The SHIFT findings do suggest that there is a role for ivabradine in patients with chronic HF, but it is not a substitute for β blocker use. There is an enormous body of evidence supporting the use of β blockers, which improve mortality as well as hospitalisation. Ivabradine should be considered only in those patients who still have a resting heart rate above 70 despite maximally tolerated doses of β blockers (or perhaps used in patients truly intolerant of β blockers). Data from 'real-world' populations of patients with HF suggest that the proportion of patients who might be eligible is low, perhaps around 5%.[40]

Iron

Is iron deficiency a target for treatment? Anaemia is very common in patients with HF,[41] but iron deficiency without anaemia is also common. The best way to manage iron deficiency is not clear: oral iron treatment is widely believed to be ineffective, yet intravenous iron treatment is also thought to be difficult or dangerous. However, a new generation of intravenous iron preparations is now available which allows both rapid and safe administration of iron to patients.

Some preliminary studies suggested that intravenous iron repletion might lead to an improvement in exercise capacity,[42] and the FAIR-HF study was designed to see if iron might be beneficial in a larger group of patients.[43] Four hundred and fifty-nine patients were randomised 2:1 to receive iron or placebo infusions (with only the patient blind to treatment). After 6 months, there was an improvement in patient self-reported global assessment (50% 'much or moderately improved', compared with 28% of patients in the placebo group) as well as in secondary end points, including distance covered in a 6 min walk test (about 40 m increase compared with no change in the placebo group). There were similar improvements regardless of starting haemoglobin.

The results have to be treated with some caution: FAIR-HF was not a large trial, blinding was difficult and the end points were to a varying degree subjective. Nevertheless, iron treatment appeared safe and is now an option for patients who remain symptomatic despite medical treatment. An absolutely essential question to answer, though, is the extent to which patients with HF should be further investigated for an underlying cause for any iron deficiency, a question not dealt with by FAIR-HF.

Another possible approach for correcting anaemia in HF is the use of erythropoiesis-stimulating proteins. A meta-analysis of six randomised controlled trials found that treatment was associated with a significantly lower risk of hospitalisation compared with placebo.[44] Mortality was unaffected. These outcomes are in contrast with studies in cancer and kidney disease and prompted the authors to a call for a large phase III morbidity and mortality trial of anaemia correction with erythropoiesis-stimulating proteins in patients with chronic HF.

Metaboličko upravljanje

Procesi stvaranja energije kod srčanih miocita koji zatajuju su abnormalni. Neki istraživači su se usredotočili na korištenje supstrata: metabolizam masnih kiselina stvara niži ATP za svaku potrošenu molekulu kisika nego metabolizam glukoze (iako se oksidacijom masnih kiselina stvara više ATP po molu) pa ima smisla pokušati promijeniti metabolizam od masnih kiselina do glukoze.[45]

Pokušani su različiti pristupi: perheksilin primjerice blokira uzimanje mitohondrijskih slobodnih masnih kiselina inhibirajući karnitin-palmitoiltransferazu. U maloj studiji perheksilin je doveo do poboljšanja mogućnosti vježbanja i funkcije lijeve klijetke te bržeg obnavljanja fosfokreatina nakon vježbe.[46] Trimetazidin inhibira beta oksidaciju lipida i njegova se primjena povezuje s povećanjem istisne frakcije lijeve klijetke i smanjenjem potrošnje energije kod mirovanja (za koju je poznato da je visoka kod ZS).[47] Meta-analiza dostupnih podataka za trimetazidin[48] također ukazuje da njegovo korištenje može dovesti do smanjenja smrtnosti te je nastulipo vrijeme za opsežnu studiju istraživanja metaboličkih modulatora.

Srčana resinhronizacijska terapija

Srčana resinhronizacija terapija (CRT: ili biventrikularni elektrostimulator) predstavlja jednu od najvažnijih novih razvojnih dostignuća za bolesnike s kroničnim ZS i blokom lijeve grane (LBBB), uvedena u posljednjih nekoliko godina. Posebno je važan njezin učinak na smanjenje smrtnosti,[49] a oko dvije trećine bolesnika imaju značajnu simptomatsku korist od uređaja.[50] Jedna trećina nema tu korist i stoga se pojavio termin 'ne reagiranja' na terapiju CRT. Kako definirati 'ne reagiranje' ovisi o pojedinim autorima, neki primjenom simptomatskih kriterija, a drugi koristeći mjere funkcije lijeve klijetke. Ono što se pokazalo teškim za odgovoriti je li "ne reakcija" vezana za nepostojanje koristi u pogledu smrtnosti.

Puno je vremena i truda uloženo da se pokuša prepoznati koji bi bolesnici mogli imati koristi od terapije CRT. Težina simptoma očito tu ne igra veliku ulogu: bolesnici s umjerenim simptomima, kako se čini, imaju jednako veliku korist kod smanjenja smrtnosti kao i oni sa lošijim stupnjem prema NYHA.[51] U studiji MADIT-CRT,[52] 1.820 bolesnika sa simptomima I ili II stupnja prema NYHA i LBBB su bili randomizirani 2:1 da dobiju (ili ne dobiju) CRT uz defibrilator. Registrirano je 34% smanjenje rizika smrti ili događaja ZS (definiranog kao kongestija liječena bilo intravenozno diureticima, nesiritidom ili inotropima više od dva sata, bez obzira na okruženje ili: povećanom dozom lijeka za ZS tijekom formalnog bolničkog prijma). Smanjenje rizika je rezultat smanjenja događaja ZS. U istraživanju RAFT,[53] koje je uključilo 1.438 bolesnika s blagim (NYHA razred II) simptomima, CRT koji je dodan defibrilatoru je doveo do smanjenja učestalosti smrtnih ishoda i hospitalizacije zbog ZS.

Drugi mogući kriterij izbora je prisutnost disinkronije u nekom obliku srčanog oslikavanja. U osnovu ovog pristupa je i pretpostavka da CRT djeluje poboljšavajući koordinaciju ventrikula, što mora biti mjerljivo na neki način. No, od velikih, randomiziranih istraživanja koja pokazuju korist kod smanjenja smrtnosti za CRT, nitko nije koristio mjere disinkronije kao ulaznog kriterija, osim manjeg broja bolesnika u studiji CARE-HF. Do sada se napori da se

Metabolic manipulation

The energy-generating processes of the failing cardiac myocyte are abnormal. Some investigators have focused on substrate use: fatty acid metabolism produces a lower yield of ATP for each molecule of oxygen consumed than glucose metabolism (although fatty acid oxidation yields more ATP per mole) and so it makes sense to try to switch metabolism from fatty acids to glucose.[45]

Various approaches have been tried: perhexiline, for example, blocks mitochondrial free fatty acid uptake by inhibiting carnitine palmitoyltransferase. In a small study, perhexiline led to improvements in exercise capacity and left ventricular function and more rapid recovery of phosphocreatine after exercise.[46] Trimetazidine inhibits lipid γ-oxidation and its use has been associated with both an increase in LV ejection fraction and reduction in resting energy expenditure (known to be high in HF).[47] A meta-analysis of the available data for trimetazidine[48] even suggests that its use might improve mortality and it is surely time for a large-scale trial of metabolic modulators.

Cardiac resynchronisation therapy

Cardiac resynchronisation therapy (CRT: or biventricular pacing) is one of the most exciting new developments for patients with chronic HF and left bundle branch block (LBBB) introduced in recent years. Particularly important is its effect on reducing mortality,[49] but around two-thirds of patients get marked symptomatic benefit from their devices.[50] That one-third do not has led to the concept of the 'non-responder' to CRT. How to define 'non-response' varies from paper to paper, with some using symptomatic criteria and others using measures of LV function. What has proved difficult to answer is whether 'non-response' is related to lack of mortality benefit.

A great deal of time and effort has been expended on trying to identify which patients might benefit from CRT. The severity of symptoms does not seem to matter greatly: those with modest symptoms appear to gain as much mortality benefit as those with worse NYHA class of symptoms.[51] In MADIT-CRT,[52] 1,820 patients with NYHA class I or II symptoms and LBBB were randomised 2:1 to receive CRT (or not) in addition to a defibrillator. There was a 34% reduction in the risk of death or a HF event (defined as congestion treated either with intravenous treatment (diuretics, nesiritide or inotrope) for more than 2 h, regardless of the setting, or: with an increased HF regimen during formal hospital admission). The reduction in risk was driven by a reduction in HF events. In RAFT,[53] which included 1,438 patients with mild (NYHA class II) symptoms, CRT added to a defibrillator led to a reduction in the rate of death and hospitalisation for HF.

Another possible selection criterion is the presence of dyssynchrony on some form of cardiac imaging. Underlying this approach is the assumption that CRT works by improving ventricular coordination, which in turn must in some way be measurable. However, of the large, randomised trials showing a mortality benefit for CRT, none used measures of dyssynchrony as an entry criterion other than a minority of patients in CARE-HF. Vigorous efforts to prove the robustness of any of the very many potential measures of dyssynchrony have failed thus far, with the PRO-

dokaže važnost bilo kojih od mnogih mjera disinkronije u PROSPECT studiji s uključenih gotovo 500 ispitanika (što je bio najveći raspoloživi skup podataka) nisu pokazali uspješnim.[54] Postojala je slaba mogućnost reproduciranja mjerenja, a niti jedna od njih nije bila snažno povezana s procjenom odgovora.

Jedini kriterij izbora koji se dosljedno smatra povezanim s ishodom su ehokardiografske varijable. Uobičajeno je zapažanje da je prosječno trajanje QRS kompleksa u istraživanjima gdje je promatrana učestalost smrtnog ishoda kod primjene CRT iznosilo oko 150 ms te u studijama gdje je bila učinjena analiza je utvrđeno da je bila veća korist što je širi QRS. Analiza podskupine iz studije PROSPECT je pokazala smanjenje simptoma uz CRT kod bolesnika s mehaničkom disinkronijom i uskim QRS kompleksom[55], a slični su rezultati objavljeni u manjim istraživanjima iz pojedinačnih centara.[56] Nema sumnje da je korist od terapije CRT uvelike ograničena na bolesnike sa LBBB,[53] i moguće je da je korist ograničena na one kojima imaju QRS >150 ms.[57]

I dok su male nerandomizirane studije objavile promjenjivu dobrobit od primjene CRT kod bolesnika s fibrilacijom atrija (AF), gotovo da nema takvih dokaza iz randomiziranih istraživanja.[58] Nekoliko istraživanja koja su uključila bolesnike s AF nisu dokazala dobrobit od primjene liječenja CRT.[53] Iako najnovije smjernice Europskog kardiološkog društva ukazuju na to bi se CRT mogao razmotriti kod bolesnika s AF,[59] razred preporuke je samo IIa, razina B ili C.

Što bi ovo sve trebalo značiti za kliničku praksu? CRT bi se trebao definitivno razmotriti za sve bolesnike sa sistoličkom disfunkcijom lijeve klijetke i simptomatskim ZS koji su u sinusnom ritmu i imaju LBBB. Terapija CRT bi se mogla pokušati kod bolesnika s perzistentnm simptomima uz AF (te LBBB), ali samo ako je frekvencija klijetki dobro kontrolirana, radi što većeg učinka elektrostimulacije. Kod takvih bolesnika obnova sinusnog ritma bolje može poboljšati kvalitetu života i funkciju lijeve klijetke[60] osiguravajući tako povoljniju reakciju na CRT.

Dalekosežnije pitanje je da li bi bolesnici sa indikacijom bradikardije za standardni imali korist od biventrikularnog elektrostimulatora. Studija s manjim brojem ispitanika, koristeći ehokardiografske ishode, ukazala je da je biventrikularna elektrostimulacija bila povezana s manjim oštećenjem funkcije lijeve klijetke.[61] Odgovor na pitanje je li veća primjena biventrikularne elektrostimulacije indicirana morat će pričekati rezultate studija s većim brojem takovih ispitanika.

Učinak programirane vježbe

Opterećenje vježbama kao standardni dio zbrinjavanja bolesnika sa kroničnim ZS se istražuje nekoliko godina.[62] Vježbanjem se nesumnjivo smanjuju simptomi bolesnika te nekoliko prediktora negativne prognoze.[63] Planiranje studije koja bi za ishod imala preživljenje smatra se teškim ne samo zbog problema oko odabira nego i zbog poteškoća s unakrsnom provjerom liječenja.

Studija HF-ACTION je randomizirala 2.331 ispitanika na uobičajenu skrb ili program intenzivnog vježbanja (36 polusatnih termina pod nadzorom tri puta tjedno, nakon čega bi uslijedile kućne vježbe umjerenog intenziteta pet puta tjedno u trajanju 40 minuta).[64] Iako primarni zajednički ishod (smrtnost svih uzroka i hospitalizacije) nije bio drugačiji između obje skupine tijekom prosječnog razdoblja praćenja od 30 mjeseci, bilo je naznake da bi program

SPECT study of nearly 500 patients being the largest available set of data.[54] There was poor reproducibility of the measures, none of which related strongly to the assessment of response.

The only selection criteria consistently shown to be related to outcome are electrocardiographic. It is a commonplace observation that the mean QRS duration in the mortality trials of CRT was around 150 ms and where it has been analysed, the broader the QRS, the greater the benefit. Subgroup analysis of PROSPECT showed some symptomatic benefit for CRT in patients with mechanical dyssynchrony and a narrow QRS complex[55] and similar findings have been reported in small single-centre trials.[56] There is no doubt, however, that the benefits of CRT are largely confined to patients with LBBB,[53] and it may even be that benefit is restricted to those with a QRS >150 ms.[57]

Similarly, while small non-randomised studies have reported variable benefit of CRT for patients in atrial fibrillation (AF), there is almost no evidence to support the practice from randomised trials.[58] The few trials that included patients in AF showed no benefit with CRT.[53] Although the European Society of Cardiology guideline updates suggest that CRT might be considered in patients in AF,[59] the class of recommendation was only IIa, level B or C.

What should all this mean in practice? CRT should certainly be considered for all patients with LV systolic dysfunction and symptomatic HF who are in sinus rhythm and have LBBB. CRT might be tried for those patients with intractable symptoms and AF (and LBBB), but only if the ventricular rate is well controlled to maximise pacing. Better still, restoration of sinus rhythm in such patients may improve both quality of life and LV function[60] while ensuring a more favourable response to CRT.

A more far-reaching question is whether patients with a standard bradycardia pacing indication would benefit from biventricular pacing. A small study using echocardiographic end points suggested that biventricular pacing was associated with less deterioration in LV function,[61] but whether widespread use of biventricular pacing is indicated will have to await the outcome of larger outcome studies.

Exercise training

The case for exercise training as a standard part of the management of patients with chronic HF has been building over several years.[62] Training undoubtedly improves patients' symptoms and several of the predictors of an adverse prognosis.[63] Mounting a properly powered survival study has proved difficult, not least because of the problems of blinding and the difficulty of cross-overs.

The HF-ACTION study managed to recruit 2,331 patients randomised to usual care or an intensive training regimen (36 supervised 30 min sessions three times a week, followed by home exercise five times a week at moderate intensity for 40 min).[64] Although the primary end point of all-cause mortality and hospitalisation was no different between the two groups at a median follow-up of 30 months, there was a signal that training might be beneficial as after adjustment for baseline differences in predictors of outcome, training was associated with an 11% reduction in the primary end point. More importantly, perhaps, training

vježbanjem mogao biti koristan poslije usklađivanja početnih razlika prediktora ishoda te je program vježbanjem bio povezan s 11% smanjenja primarnog ishoda. Što je važnije, možda je programirano vježbanje bilo povezano sa značajnim unaprjeđenjem kvalitete života što se pojavilo u ranom fazi tijekom intervencije i nastavilo tijekom studije.[65]

Još uvijek je nejasno je li je vrsta opterećenja važna: većina dokaza se odnosni na aerobne vježbe. Noviji pregledni članak o treningu jakosti je pokazao da je kvaliteta studija loša i učinci su bili neuvjerljivi za ishode kvalitete života.[66]

Teško je uključiti program vježbanja u standardno zbrinjavanje ZS.[62] Suradljivost pacijenta će uvijek biti izazov — čak i u studiji HF-ACTION nakon godinu dana suradljivost pacijenata je iznosila samo oko 80%. Iako je vježbanje kod kuće sigurno,[64] početno nadziranje može biti od pomoći za bolesnike i njihove njegovatelje te su implikacije za izvor zdravstvenih sredstava od velike važnosti. Je li program treninga moguć za mnoge bolesnike koji su stariji, krhki i s više kormobiditeta premet je rasprave. U svakom slučaju bolesnike treba uvjeriti da je vježba sigurna i da će dovesti do smanjenja simptoma.

Revaskularizacija

Najčešći uzrok ZS je ishemijska bolest srca. Nema uvjerljivih podataka da je liječenja usmjereno na ishemiju primjerice statinima,[67] korisno, usprkos intuitivnom osjećaju da bi liječenje ishemije trebalo biti učinkovito. Je li revaskularizacija bolesnika sa ZS no bez angine mogla biti od koristi predstavlja jedno od izazovnijih pitanja. Opservacijske studije ukazuju da bi se revaskularizacijom mogla poboljšati prognoza, posebice kod onih s dokazivom vijabilnosti na funkcijskom testiranju,[68] ali sada postoje dvije randomizirane studije u kojima se ovaj problem izravno ispituje.

U studiji HEART,[69] bolesnici sa ZS te viabilnim, ali disfunkcionalnim, miokardom bili su randomizirani u dvije strategije: konzervativno zbrinjavanje ili angiografija uz razmatranje revaskularizacije. Nije bilo razlike u preživljenju između obje skupine tijekom razdoblju od 59 mjeseci. Iako je proces uključenja u studiju tekao sporo i uključeno je samo 138 od planiranih 800 pacijenata, nije bilo pokazatelja koji bi ukazivao na dobrobit.

U studiju STICH[70] bilo je uključeno 1.212 bolesnika sa istisnom frakcijom ≤35% koji su se smatrali prikladnima za implantaciju aortokoronarnog premoštenja (CABG). Bolesnici su bili randomizirani na liječenje primjenom CABG ili farmakološki. Tijekom prosječnog razdoblja praćenja od 56 mjeseci, nije bilo razlike u primarnom ishodu (smrtnosti od svih uzroka) između obje skupine. Zajednički ishod (svi uzroci smrtnosti i kardiovaskularna hospitalizacija) bila je smanjena u skupini CABG, ali analiza je isključila hospitalizaciju zbog operativnog zahvata koja nije zanemariv događaj: 60 hospitalizacija spriječenih primjenom CABG je zahtjevalo 555 hospitalizacija radi liječenja primjenom CABG.[71] Bilo je više smrtnosti u CABG skupini u razdoblju od više od dvije godine nakon randomizacije, naglašavajući da ovaj postupak nije benigna intervencija.

Zajedno studije HEART i STICH pokazuju da postoji granična dobrobit za revaskularizaciju kod bolesnika sa ZS uz ishemijsku bolest srca. Kako bi rezultati bili povezani s kliničkom praksom nije jasno: u studiji STICH, prosječna dob bolesnika je bila oko 60 godina, srčana frekvencija u mirovanju je bilo >70/min (sugerirajući vjerojatno neadekwas associated with a marked improvement in quality of life, which appeared early during the intervention and continued throughout the course of the study.[65]

It is still unclear whether the type of training stimulus is important: most evidence relates to aerobic training. A recent systematic review of trials of resistance training found that the quality of the studies has been poor and effects were inconclusive for quality-of-life outcomes.[66]

Incorporating exercise training into standard HF management is difficult.[62] Compliance will always be a challenge-even in HF-ACTION, and after a year, patients' compliance with exercise was only about 80%. Although home exercise is safe,[64] initial supervision may be helpful for both patients and their carers and the resource implications are substantial. Whether a training programme is possible for many patients, who may be elderly, frail and have multiple comorbidities, is debatable. Nevertheless, patients can be reassured that exercise is safe and will improve their symptoms.

Revascularisation

The commonest cause of HF is underlying ischaemic heart disease. However, there is no good evidence that treatments directed at ischaemia with, for example, statins,[67] are beneficial, despite the intuitive feeling that treating ischaemia should be effective. One of the more challenging questions has been whether revascularisation for patients with HF and no angina might be beneficial. Observational studies suggest that revascularisation might indeed improve prognosis, particularly in those with demonstrable viability on functional testing,[68] but we now have two randomised trials that examine the problem directly.

In HEART,[69] patients with HF and viable but dysfunctional myocardium were randomised to two strategies of care: conservative management or angiography with a view to revascularisation. There was no difference in survival between the two groups at 59 months. Although the trial recruited slowly and only 138 of the planned 800 patients were enrolled, there was no signal suggesting benefit.

STICH[70] included 1,212 patients with an ejection fraction ≤35% who were considered suitable for coronary artery bypass grafting (CABG). The patients were randomised to CABG or continued medical treatment. Over a median follow-up of 56 months, there was no difference in all-cause mortality, the primary end point, between the treatment groups. The combined end point of all-cause mortality and cardiovascular hospitalisation was reduced in the CABG group, but the analysis excludes hospitalisation for the original operation, which is scarcely a negligible event: the 60 hospitalisations prevented by CABG required 555 hospitalisations for the CABG procedure itself.[71] There were more deaths in the CABG group for more than 2 years after randomisation, emphasising that this is not a benign intervention.

Together, HEART and STICH show that there is, at most, a marginal benefit for revascularisation in patients with HF and underlying ischaemic heart disease. How the results relate to clinical practice is not clear: in STICH, the average age of patients was around 60, resting heart rate was >70 (suggesting, perhaps, inadequate β blockade) and fewer

vatnu beta-blokadu) te manje od 10% je imalo kroničnu bubrežnu insuficijenciju (vrijednost kreatinina nije navedena u članku). Usprkos ogromnom naporu utrošenom da bi se odgovorilo na pitanje, još uvijek nije jasno je li revaskularizacija od koristi za bolesnike sa ZS.

Akutno zatajivanje srca

Nakon mnogo godina kliničkih istraživanja kod bolesnika sa kroničnim ZS, ponovno se javlja interes za problem akutnog ZS — djelomično i zbog dostupnosti novih lijekova za moguće liječenje.

Jedan od najčešće korištenih novih lijekova za akutno ZS je nesiritid, licenciran za primjenu u SAD, uglavnom kao rezultat istraživanja koja su ukazala na određena hemodinamska poboljšanja.[72] Sa europskog stajališta uvijek je izgledalo pomalo čudno da se nesiritid široko primjenjivao, no da Europska agencija za lijekove nije dopuštala njegovu primjenu u EU. Istraživanje koje je uključilo 7.000 bolesnika uspoređujući nesiritid s placebom uz standardno liječenje je sada dovršeno.[73] Nije pronađena statistički značajna razlika u prisutnosti simptoma između ove dvije skupine, kao niti u ponovnoj hospitalizaciji ili u smrtnom ishodu u razdoblju praćenja od 30 dana.

Drugo sredstvo za moguću primjenu kod bolesnika sa akutnim ZS je rolofilin, antagonist adenozina. Rolofilin bi mogao pomoći u prevenciji smanjenja bubrežne funkcije tijekom liječenja diureticima prekidajući glomerulotubularne reakcije. No, u studiji koja je uključila 2.000 bolesnika, rolofilin nije imao nikakvog učinka na primarni ishod (složeni rezultat "uspjeha liječenja"), bubrežnu funkciju ili smrtnost.[74-75]

Sveukupno, istraživanja rolofina i nesiritida naglašavaju važnost odgovarajuće primjene kliničkih istraživanja radi poboljšanja liječenja. Oslanjanje na istraživanja s relativno malim brojem ispitanika s neodgovarajućim ishodima su dovela do debakla nesiritida, dok je istraživanje rolofina uslijedilo nakon određenog niza ranih manjih studija koje su dale informacije o dizajnu prikladnih studija.

Pravilno doziranje diuretika kod bolesnika zaprimljenih radi zadržavanja tekućine je često bilo predmetom kontroverzi. Studija DOSE[76] je bila dizajnirana da bi pružila odgovor na ovaj aspekta zbrinjavanja akutnog ZS. Bilo je randomizirano 380 ispitanika s retencijom tekućine zbog ZS na liječenje furosemidom bilo kao bolus dozu svakih 12 sati ili kao kontinuiranu infuziju: obje strategije su primjenjene kao niska ili visoka doza lijeka. Postojala su dva su-primarna ishoda: procjena globalnih simptoma nakon 72 sata od strane pacijenta i promjena vrijednosti kreatinina od početnih vrijednosti do nakon 72 sata. Nije bilo značajne razlike između primjene bolusa i infuzije, ali je uočeno nešto veće (no statistički neznačajano) poboljšanje simptoma kod skupine se visokom nasuprot skupine s niskom dozom. Skupine koje su liječene visokom dozom su imale značajno veću diurezu.

Teško je izravno uspoređivati praksu u SAD i Europi. Tipično su bolesnici sa akutnim ZS u bolnici oko pet dana u SAD, no 11 dana u Europi i bilo kakav gubitak na težini tijekom hospitalizacije (zbog gubitka tekućine) je puno manji, što znači da se bolesnici u SAD hospitaliziraju s puno manje preopterećenja tekućinom, nego u Europi. Postoje li razlike između primjene furosemida u bolusu ili kon-

than 10% had 'chronic renal insufficiency' (creatinine is not reported in the paper). Despite the enormous effort expended to answer the question, it is still not clear whether revascularisation is helpful for patients with HF.

Acute HF

After many years of clinical trials in patients with chronic HF, there has been renewed interest in the problem of acute HF-in part, driven by the availability of new drugs as potential treatments.

One of the most widely used new treatments for acute HF has been nesiritide, licensed for use in the USA, largely as a results of trials showing some improvement in haemodynamics.[72] It has always seemed a little strange from a European perspective that nesiritide has been so widely used and the European Medicines Agency did not allow its use in the EU. A 7,000 patient trial comparing nesiritide with placebo in addition to standard treatment has now been completed.[73] No statistically significant difference in symptoms scores was found between the two groups, or in rehospitalisation or death at 30 days.

Another agent for possible use in patents with acute HF is rolofylline, an adenosine antagonist. Rolofylline might help to prevent decline in renal function with diuretic treatment by interrupting glomerulotubular feedback. However, in a 2,000 patient study, rolofylline had no effect on the primary end point (a composite 'treatment success' score), renal function or mortality.[74,75]

Taken together, the trials of rolofylline and nesiritide highlight the importance of using clinical trials appropriately to drive the evolution of treatment. Reliance on relatively small trials with inappropriate end points led to the nesiritide deb,cle, whereas investigation of rolofylline followed an appropriate sequence with early small-scale studies informing the design of a properly powered endpoint study.

The correct diuretic dosing regimen for patients admitted with fluid retention has often been a controversial question and the DOSE trial[76] was designed to help guide this aspect of acute HF management. Three hundred and eight patients with fluid retention due to HF were randomised to receive furosemide either as a bolus every 12 h or by continuous infusion: both were given as either low or high dose. There were two co-primary end points: patients' global symptom assessment over 72 h and change in creatinine level from baseline to 72 h.

No significant difference was found between bolus and infusion regimens, but a small (and statistically non-significant) greater improvement in symptoms in the high-dose versus low-dose groups was seen. The high-dose groups had a substantially greater diuresis.

It can be difficult directly to compare practice in the USA with Europe. Typically, patients with acute HF are in hospital for around 5 days in the USA, but 11 days in Europe and any acute weight loss during admission (presumably reflecting fluid loss) is very much smaller, implying that patients are admitted in the USA with very much less fluid overload than in Europe. Whether there are differences between furosemide given by bolus or continuous infusion over a longer time scale cannot be addressed by DOSE, but the message that high doses of furosemide (de-

tinuiranom infuzijom tijekom dužeg vremenskog razdoblja nije se razrješilo studijom DOSE, ali je jasna poruka da visoke doze furosemida (definirane ovdje kao 2.5 veće od uobičajene oralne doze bolesnika) uzrokuju veću diurezu.

fined here as 2.5 times the patient's usual oral dose) cause a greater diuresis is clear.

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