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Almanah 2013.: zatajivanje srca

Almanac 2013: heart failure

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EPIDEMIOLOGIJA, NACIONALNI REGISTAR I SMJERNICE

Nacionalni registar zatajivanja srca predstavlja važan izvor informacija o zbrinjavanju akutnog zatajivanja srca (ZS) u Engleskoj i Walesu. Posljednje izvješće[1] navodi nešto više od 37.000 hospitalizacija. Kao i u prethodnom, manje od polovice bolesnika liječeni su na kardiološkim odjelima i imali su bolji ishod; polovica je upućena na daljnje kontrole kardiologu što je rezultiralo boljim ishodom. Inovacija registra je analiza podataka na bolničkoj razini. Neumjesno bi bilo odabrati imena, no uočljiva je promjenjiva učestalost primjene osnovnih varijabli poput ehokardiografije, dostupnost kardiologa u zbrinjavanju bolesnika i učestalost propisivanja različitih lijekova.

Istraživanja pokazuju da su tijekom dugotrajnog praćenja bolesnika od strane specijalista za ZS, uključujući i medicinske sestre specijalizirane za ZS, pacijenti bili adekvatnije liječeni odgovarajućim lijekovima u odgovarajućoj dozi te imaju nižu stopu re/hospitalizacije i bolju prognozu[2]. Prema postojećim dokazima rezultati su bolji ako je dio multidisciplinarne intervencije izvršen u kući.[3] Postoje čvrsti dokazi da specijalističke klinike smanjuju rizik od ponovne hospitalizacije zbog ZS odmah nakon početnog prijma.[4]

Za kliničku praksu dostupne su smjernice o ZS od Nacionalnog instituta za zdravlje i kliničku izvrsnost (NICE)[5,6] te pripadajući standardi kvalitete[7]. Standardi NICE jasno ukazuju čemu NHS usluge diljem Engleske i Walesa trebaju težiti. Zajedno s analizom registra bolničke razine, standardi kvalitete trebali bi timovima za ZS u primarnoj i sekundarnoj skrbi osigurati informacije o zbrinjavanju ove bolesti.

Postaje sve jasnije da će postupci koji se koriste sada za zbrinjavanje ZS vjerojatno biti neprimjereni u budućnosti: u američkoj studiji[8] predviđa se da će se troškovi zbrinjavanja ZS više nego udvostručiti do 2030. godine, uglavnom zbog starenja populacije. Kapacitet zdravstvene službe za zbrinjavanje sve većeg broja pacijenata nije neograničen. Dio rješenja bit će promjena u cilju veće učinkovitosti korištenja ograničenih resursa, no važan čimbenik bit će smanjenje rizika za razvoj ZS. Olakšanje mnogim liječnicima čini se predstavlja kava koja pruža neki stupanj zaštite.[9]

Najnovije smjernice Europskog kardiološkog društva iz 2012. godine[10] spajaju zbrinjavanje akutnog i kroničnog ZS. I dalje se naglašava središnja uloga ispitivanja natrijuretskih

EPIDEMIOLOGY, THE NATIONAL AUDIT AND GUIDELINES

The National Heart Failure Audit continues to be an invaluable resource for understanding how acute heart failure is managed in England and Wales. The most recent report[1] describes just over 37 000 hospitalisations. As in previous publications, fewer than half the patients were managed in cardiology wards, yet those who were had a better outcome; half were referred at discharge to cardiologists for follow-up and they, too, had a better outcome. An innovation in the audit this time was the publication of hospital level analysis. It would be invidious to pick out names, but it is very striking how variable are the rates of such basic items as the use of echocardiography, availability of a cardiologist to manage the patients and the rate of prescription of different drugs.

Studies show that, during long-term follow-up, patients managed by heart failure specialists including 'heart failure nurses' are more likely to be treated with the appropriate medication in the appropriate dose, have lower (re-)admission rates to hospital and a better prognosis.[2] There is reason- able evidence that there are better outcomes if part of the multidisciplinary intervention is made in the home.[3] There is strong evidence that specialist clinics reduce the risk of readmission with heart failure immediately after an index admission.[4]

Also available to the clinician are the heart failure guidelines from the National Institute for Health and Care Excellence (NICE)[5,6] and the associated quality standards.[7] The NICE standards make it clear what NHS services across England and Wales should be striving towards. Combined with the hospital level analysis from the audit, the quality standards should give clinical teams the ammunition they need when discussing their heart failure service with management teams in both primary and secondary care.

However, it is becoming ever clearer that the systems used for managing heart failure at present are unlikely to be adequate in future: a study from the USA[8] predicts that the costs of managing heart failure will more than double by 2030, mainly due to the ageing of the population. The capacity of the health service to accommodate the increasing numbers is not infinite. Part of the solution will surely have to be a change towards greater efficiency of use of limited resources, but reducing the risk of developing heart failure will also be a major contributor. Of some relief to many doctors, coffee appears to offer some protection.[9]

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peptida u dijagnostici — još uvijek nije univerzalno dostupan u Velikoj Britaniji, ali ima ključnu ulogu u NICE preporukama. U smjernicama se naglašava važnost primjene antagonista mineralokortikoidnih receptora koji bi trebali postati dio standardne terapije za svakoga pacijenta sa simptomatskim ZS te bi se trebali koristiti kao dodatna terapija ACE inhibitorima i beta-blokatorima.

AKUTNO ZATAJIVANJE SRCA

Dugi niz godina naglasak u istraživanjima ZS bio je na bolesnicima s kroničnim stabilnim ZS. Vrlo je malo novih podataka u području akutnog oblika bolesti. Istraživanja kod bolesnika s akutnim ZS je teško: imaju akutno stanje, često usred noći, iznimno loše prognoze. Klinička istraživanja prihvatila su izazov 'standardnog" zbrinjavanje akutnog ZS.

Precipitirajući čimbenici za hospitalizaciju pacijenta sa ZS predstavljaju progresija osnovne bolesti, ishemijski događaj ili aritmija. Lista precipitirajućih čimbenika često navodi uzrokom i okoliš, bez dodatnog objašnjenja. Sada postoje čvrsti dokazi, pa su tako u meta-analizi *Shaha i sur.*[11], otkrivena značajna povezanost između rizika hospitalizacije zbog ZS i smrti s mnogim onečišćivačima okoliša, uključujući ugljikov monoksid, sumporni dioksid, dušikov dioksid i pojedine čestice. Postoji javnozdravstveni interes za smanjenje onečišćenja okoliša, a sada su vidljive ekonomske posljedice onečišćenja okoliša mjerljive brojem hospitalitacija radi ZS.

Zbrinjavanje viška tekućine

Podaci nacionalnog registra ukazuju na činjenicu da oko polovica hospitaliziranih bolesnika sa ZS ima umjerenu ili težak stupanj retencije tekućine. Tradicionalno liječenje uključuje ograničenje tekućine (često s ograničenjem soli), no izuzetno malo dokaza potvrđuje učinkovitost ove preporuke. U maloj i intrigantnoj studiji, *Aliti i sur*[12] randomizirali su 75 bolesnika s radikalnim ograničenjem tekućine (800 ml/dan) i ograničenjem natrija (800 mg/dan) u odnosu na terapiju bez takvog ograničenja. Nije bilo rezultata u kliničkim ishodima studije (posebice mršavljenja i učestalosti rehospitalizacije u razdoblju od 30 dana), ali ograničenje tekućine dovelo je do veće žeđi. Navedeno istraživanje nije definitivan dokaz, ne osporava standardnu praksu, ali treba provesti veća istraživanja.

Standardna terapija liječenja retencije tekućine je intravenozna primjena diuretika, uz čestu primjenu infuzija tijekom nekoliko dana. Moguće je primijeniti ultrafiltraciju radi bržeg uklanjanja tekućine, a rani rezultati istraživanja provedenog kod 200 bolesnika dokazali su da se, u usporedbi sa standardnom terapijom, ultrafiltracijom može smanjiti potreba za dolaskom u hitnu službu bolesnika sa ZS unutar 3 mjeseca nakon otpusta.[13] U istraživanju CARRESS-HF praćeni su učinci ultrafiltracije kod 188 bolesnika s retencijom tekućine uslijed ZS i pogoršanja bubrežnog zatajivanja. Primarni ciljevi bili su sniženje razine kreatinina i tjelesne težine unutar 96 sati. Bubrežna funkcija kod ispitanika ne očekivano se pogoršala više u ultrafiltracijskoj skupini nego onih na standardnoj terapiji. Među ispitivanim skupinama nije bilo razlike u smrtnosti ili učestalost rehospitalizacija unutar 90 dana.

Teško je interpretirati ove podatke. Bolesnici u CARESS-HF razlikovali su se od ispitanika u studiji UNLOAD jer su već na početku ispitivanja imali viši rizik zbog kronične bubrežne bolesti. Unatoč činjenici postojanja 'perzistentne kongestije' i pogoršanja bubrežne funkcije na početku studije (prosječni

The latest guidelines from the European Society of Cardiology were published in 2012, merging the management of acute and chronic heart failure.[10] They continue to emphasise the central role of natriuretic peptide testing for diagnosis — which is still not universally available in the UK but a key part of the NICE recommendations. The guidelines emphasise that mineralocorticoid receptor antagonists should now be considered to be part of standard therapy for anyone with symptomatic heart failure and should be used in preference to angiotensin receptor blockers as add-on therapy ACE inhibitors and beta-blockers.

ACUTE HEART FAILURE

For many years the focus of heart failure research has been on patients with chronic stable heart failure. There has been little new for acute heart failure for many years. Recruiting patients with acute heart failure is difficult: they present acutely, often in the middle of the night, and are often extremely unwell. However, clinical trials are now reporting which are starting to challenge the 'standard' management of acute heart failure.

Common precipitants of an admission to hospital with heart failure include intercurrent illness, an ischaemic event or an arrhythmia. Lists of precipitants often quote 'environment' without specifying further what that might mean; but now we have some hard evidence. In a meta-analysis, *Shah and al*[11] found very strong relations between the risk of both hospitalisation for heart failure and death and many environmental pollutants including carbon monoxide, sulfur dioxide, nitrogen dioxide and particulate matter. There is a clear public health interest in reducing environmental pollution, and we can now see the economic consequences of pollution in terms of heart failure admissions.

Fluid management

Data from the national audit suggest that around half of patients admitted to hospital with heart failure have moderate or severe fluid retention. Traditional management has been by fluid restriction (often with salt restriction), but there is remarkably little evidence to show that this treatment is effective. In a small but intriguing study, *Aliti et al*[12] randomised 75 patients to a radical fluid-restricted (800 mL/day) and sodium-restricted (800 mg/day) regime versus no such restriction. There was no effect of the restricted diet on clinical outcomes (particularly weight loss and readmission rates at 30 days), but the fluid restriction led to greater thirst. While this is certainly not definitive evidence, it does challenge standard practice and should lead to larger trials.

The standard therapy for fluid retention is intravenous diuretic use, often using infusions over several days. It might be possible to use ultrafiltration to remove fluid more rapidly, and an early trial of 200 patients suggested that ultrafiltration might reduce the need for emergency attendances with heart failure up to 3 months after discharge compared with standard therapy.[13] In CARRESS-HF, however, the effects of ultrafiltration in 188 patients with the combination of fluid retention due to heart failure and worsening renal failure were studied. The primary endpoint was creatinine and weight loss at 96 h. Perhaps surprisingly, renal function deteriorated more in the ultrafiltration group than with standard therapy. There was no difference between the groups in either mortality or 90-day readmission rate.

It is difficult to know how to interpret these data. The patients in CARESS-HF differed from those in UNLOAD, being at much higher risk because of their renal failure at baseline.

kreatinin na početku μ180 mol/L), pacijenti kojima je primjenjena standardna terapija izgubili su više od 4 kg na tjelesnoj težine bez promjene koncentracije kreatinina unutar 96 sati. Pacijenti kojima je primjenjena ultrafiltracija imali su slično smanjenje tjelesne težine. Porast kreatinina za oko 20 μmol/L s metodom ultrafiltracijom može predstavljati hemokoncentraciju, a ne značajnu promjenu bubrežne funkcije. Ultrafiltracija i dalje predstavlja mogućnost bržeg uklanjanja tekućine kod bolesnika sa ZS (medijan bolničkog liječenja je oko 11 dana), no njegova točna uloga još nije definirana.

Relaksin

Bilo je mnogo očekivanja od serelaksina, humanog rekombinantnog relaksina-2. Relaksin je uglavnom poznat po djelovanju u trudnoći, uzrokuje arterijsku vazodilataciju s malo učinka na venodilataciju. Manje istraživanje potrebne doze lijeka ukazalo je na mogućnost smanjivanja zaduhe u bolesnika s akutnim ZS, s mogućim poboljšanjem ishoda.[14] U istraživanju RELAX-AHF[15] 1.161 ispitanik s akutnim ZS liječen je 48-satnim infuzijama placeba ili serelaksina. Ispitanici u skupini liječenih serelaksinom imali su blago smanjenje zaduhe, jedan do dva stupnja. Registrirano je smanjenje šestomjesečne smrtnosti kod skupine na sereleksinu u usporedbi s placebom.

Nije još jasno kako će istraživanje biti primjenjivo u kliničkoj praksi. Američka agencija za hranu i lijekove označila je serelaksin kao 'revolucionarno liječenje'[16] upućujući na činjenicu da serelaksin predstavlja značajan napredak u odnosu na trenutno dostupnu terapiju, no podaci iz studije RELAX-AHF nisu uvjerljivi. U studiji je zabilježen mali broj događaja, čini se da serelaksin nema nikakvog utjecaja na druge ishode, a uspoređivan je s placebom (a ne drugi vazodilator poput nitrata). Ipak, ako se rezultati potvrde u daljnjim ispitivanjima, serelaksin može predstavljati prvi veliki iskorak u liječenju akutnog ZS u predstojećem razdoblju.

Inhibicija neprilizina

LCZ696 prvi je u klasi lijekova pod nazivom ARNIs odnosno, kombinirani antagonist receptora angiotenzina II (valsartan) s inhibitorom neprilizina. Neprilizin je enzim odgovoran za razgradnju natrijuretskih peptida, njegova blokada povećava količinu natrijuretskog peptida u cirkulaciji. U istraživanju PARAMOUNT[17] ukupno je 301 ispitanika sa ZS i urednom ejekcijskom frakcijom bilo randomizirano za primjenu kombiniranog inhibitora ili samog valsartana. Primjena LCZ696 rezultirala je većim padom NT-proBNP u 12 tjednu (učinak izgubljen do 36 tjedna), a zabilježeno je i smanjenje simptoma. Pozitivni rezultati vjerojatno će dovesti do velikih studija, iako će biti problema u izboru usporedbe za LCZ.[18]

Levosimendan

Konačno su objavljeni rezultati REVIVE studije koja ispituje učinke levosimendana kod bolesnika s akutnim ZS, oko osam godina nakon što je prvi put predstavljena.[19] Levosimendan je senzibilizator kalcija kojima inotropne i vazodilatatorne učinke. U početku je bilo puno entuzijazma glede moguće uloge u akutnom ZS, a u istraživanju REVIVE registrirano je kliničko poboljšanje nakon levosimendana. Međutim, postojao je i povećan rizik smrtnog ishoda, iako neznačajan u skupini na levosimendanu.

Kašnjenje u objavljivanju rezultata studije ističe važno pitanje istraživanja, odnosno mogu li neutralni ili negativni rezul-

Despite the patients at trial entry having 'persistent congestion' and worsening renal function (mean creatinine at trial entry 180 μmol/L), those randomised to standard therapy lost over 4 kg in weight with no change in creatinine at 96 h. Those randomised to ultrafiltration had a similar weight loss. It may simply be that the rise in creatinine of around 20 μmol/L with ultrafiltration represented haemoconcentration rather than reflecting any significant change in renal function. Ultrafiltration holds out the hope of more rapid removal of fiuid for patients with heart failure (the median length of stay for fiuid retention remains around 11 days), but its precise role has still not been defined.

Relaxin

There has been much excitement about serelaxin, human recombinant relaxin-2. Relaxin is mainly known for its effect in pregnancy, but it causes arterial vasodilation with little effect on venodilation. A small dose-finding trial suggested that it might lead to more rapid relief of breathlessness in patients with acute heart failure, with a suggestion that it might improve outcome.[14] In the RELAX-AHF trial,[15] 1,161 patients with acute heart failure were randomised to receive 48 h infusions of placebo or serelaxin. The serelaxin-treated patients had a modest improvement in their breathlessness, but only in one of the two scales used. More interestingly, though, there was a reduction in mortality at 6 months in the serelaxin group com- pared with placebo.

How this will translate into clinical practice is not at all clear. Although the Food and Drug Administration in the USA has given serelaxin 'Breakthrough Therapy' designation,[16] suggesting that they believe serelaxin represents 'a substantial improvement over currently available therapies', the data from RELAX-AHF are not convincing. There were only a small number of events, serelaxin appeared to have no effect on other events, and the comparator limb of the trial was placebo (and not another vasodilator such as a nitrate). Nevertheless, if the results are confirmed in further trials, serelaxin may represent the first major step forward in treating acute heart failure in many years.

Neprilysin inhibition

LCZ696 is the first in a new class of drugs termed ARNIs, that is a combined angiotensin II receptor antagonist (valsartan) with a neprilysin inhibitor. Neprilysin is the enzyme responsible for the breakdown of natriuretic peptides, so its blockade increases the amount of natriuretic peptide in the circulation. In the PARAMOUNT trial,[17] 301 patients with heart failure and a normal ejection fraction were randomised to receive the combined inhibitor or valsartan alone. Those receiving LCZ696 had a greater decline in N-terminal prohormone of brain natriuretic peptide at 12 weeks (an effect lost by 36 weeks), and there was greater improvement in symptoms. The positive results will probably trigger a large outcome study, although there will be problems in knowing what the comparator to LCZ might be.[18]

Levosimendan

The REVIVE studies testing the effects of levosimendan in patients with acute heart failure have finally been published, around 8 years after they were first presented.[19] Levosimendan is a calcium sensitising drug — it has inotropic and vasodilator effects. There was much initial enthusiasm over its possible role in acute heart failure and, in REVIVE, there was a greater likelihood of clinical improvement with levosimendan. However, there was an increased risk of death, albeit non-significant, in the levosimendan group.

tati ostati neobjavljeni. Levosimendan je je široko dostupan u Europi, no njegove potencijalno štetne posljedice ne mogu biti prepoznate. Provedena klinička ispitivanja nose moralnu obvezu objavljivanja podataka: bolesnici su pristali sudjelovati u kliničkim ispitivanjima kako bi rezultati mogli koristiti drugima.[20]

KRONIČNO ZATAJIVANJE SRCA

Ivabradin

SHIFT studija[21] ukazuje na činjenicu da se dodatkom ivabradina, koji usporava srčanu frekvenciju inhibiranjem depolarizacije sinusnog čvora, poboljšavaju ishodi u bolesnika sa ZS zbog sistoličke disfukcije lijeve klijetke sa sinus ritmom i uz frekvenciju ≥70/min. Pozitivan ishod studije potvrđuje smanjenje broja hospitalizacija uslijed ZS, ali je post hoc analiza ukazala na moguću dobrobit preživljenja bolesnika s frekvencijom srca u mirovanju ≥75/min.[22]

Procjena ivabradina u NICE[23,24], preporuča ga kao dodatak za bolesnike s frekvenciom srca u mirovanju ≥75/min, koji su već na standardnoj terapiji (uključujući prikladan beta-blokator na maksimalno podnošljivoj dozi), ali naglašava da bi se liječenje s ivabradinom trebalo započeti po preporuci specijalista za srčano zatajivanje. Potreba za praćenjem od specijaliste naglašava se kao nedostatak, obzirom na činjenicu da bi ivabradin mogao postati prihvatljiva alternativa beta-blokatorima za čiju primjenu postoje dokazi o poboljšanju preživljavanja.

U raspravi o ivabradinu naglašava se velika važnost smanjenja frekvencije srca kao terapijskog cilja. Izazovna je ponovna interpretacija podataka iz istraživanja DIG, koji pokazuje da je digoksin u bolesnika sa ZS u sinusnom ritmu imao slični učinak na zajedničke ishode koji su praćeni u SHIFT studiji (kardiovaskularna smrt ili hospitalizacija zbog srčanog zatajivanja) kao ivabradin, s djelovanjem na smanjenje hospitalizacije, a ne povećanja preživljavanja.[25] Iako je primjena digoksina u današnje vrijeme vrlo varijablina, može se dogoditi ćemo ga ponovno primijenjivati kao lijek za redukciju srčanog ritma.

Aliskiren

Inhibicija renin-angiotenzin-aldosteron sustava (RAAS) je imala vrlo značajnu ulogu u zbrinjavanju ZS već desetljećima, no, iako su glavne značajke sustava dobro poznate, posljedice RAAS još uvijek nisu u cijelosti otkrivene. Primjerice, angiotenzin II (Ang II) se može razdijeliti pomoću ACE2 do Ang1-7, koji i sam ima biološku aktivnost.[26] Postoje mnogi potencijalni ciljevi za liječenje koji postaju dostupni. Jedan takav potencijalni cilj je početni korak u kaskadi — inhibicija enzimske aktivnosti samog renina.

Aliskiren je izravan inhibitor renina. Rani radovi ukazivali su na to da bi aliskiren mogao imati veći utjecaj na suzbijanje proizvodnje natrijuretskog peptida nego standardna terapija,[27] a njegova sposobnost da izbjegne bijeg od ACE inhibicije čini ga atraktivnim sredstvom. Međutim, dva istraživanja su bacila sumnju na njegovu učinkovitost. U istraživanju ALTITUDE[28] 8.561 bolesnika s dijabetesom, kroničnom bolesti bubrega i/ili kardiovaskularnom bolesti bili su randomizirani na aliskiren ili placebo uz standardnu terapiju. Istraživanje je zaustavljeno odmah nakon privremene analize o učinkovitosti, jer je postojala naznaka (iako ne i statistički značajna) da bi aliskiren mogao biti štetan. U studiji ASTRONAUT[29,30] 1.639 bolesnika bilo je randomizirano na aliskiren ili placebo

The delay in publication highlights a very important issue in clinical trials-namely, that neutral or negative trials might go unreported. Levosimendan has been widely available in Europe, but its potentially deleterious effects may not be recognised by those using it. Those designing and running clinical trials have a moral obligation to publish their data: patients have, after all, agreed to take part in clinical trials on the basis that the results may benefit others.[20]

CHRONIC HEART FAILURE

Ivabradine

The SHIFT study[21] suggested that the addition of ivabradine, which slows the heart rate by inhibiting sinus node depolarisation, improves outcomes in patients with heart failure due to left ventricular systolic dysfunction, in sinus rhythm and with a heart rate ≥70/min. The benefit seen was largely a reduction in hospitalisation for heart failure, but a post hoc analysis suggested that there may be a survival benefit for patients with a resting heart rate ≥75/min.[22]

A single technology assessment of ivabradine by NICE[23,24] recommends ivabradine as an adjunct for patients with a resting heart rate ≥75/min who are already on standard therapy (including appropriate beta-blocker at the maximally tolerated dose), but goes on to suggest that ivabradine should only be started by a heart failure specialist. The need for a specialist goes some way to addressing the major concern that ivabradine might come to be seen as an acceptable alternative to beya-blockers when the evidence that beta-blockers improve survival is overwhelming.

The ivabradine discussion highlights the potential importance of heart rate reduction as a therapeutic target. A challenging reinterpretation of the data from the DIG trial suggests that digoxin in patients with heart failure in sinus rhythm had a similar reduction in the endpoint used in the SHIFT study (namely, cardiovascular death or hospitalisation for heart failure) as ivabradine, with the effect being a reduction in hospitalisation rather than an increase in survival.[25] Although digoxin is very variably used nowadays, it may be that we should be revisiting its use as heart rate-reducing agent.

Aliskiren

Inhibition of the renin-angiotensin-aldosterone system (RAAS) has been the cornerstone of heart failure management for decades but, although the outlines of the system are well known, the full ramifications of the RAAS are still being uncovered. For example, angiotensin II (Ang II) can be broken down by ACE2 to yield Ang1-7, which itself has biological activity.[26] There are many potential targets for treatment becoming available. One potential target has been the initial step in the cascade — inhibition of the enzymatic activity of renin itself.

Aliskiren is a direct renin inhibitor. Early work suggested that it might have a more profound effect on suppressing natriuretic peptide production than standard therapy,[27] and its ability to avoid any escape from ACE inhibition makes it an attractive agent. However, two trials have cast doubt on its effectiveness. In the ALTITUDE trial,[28] 8,561 patients with diabetes, chronic kidney disease, cardiovascular disease or both were randomised to receive aliskiren or placebo in addition to standard therapy. The trial was stopped early after an interim efficacy analysis, and there was a suggestion (although not statistically significant) that aliskiren might be

bo, uz standardnu terapiju, oko petog dana nakon prijma zbog ZS. Nije bilo učinka na zajednički primarni ishod (kardiovaskularna smrti ili ponovna hospitalizacija radi ZS nakon 6 i 12 mjeseci), ali je postojao definitivan znak da bi aliskiren mogao biti štetan u bolesnika s dijabetesom.

Studija ATMOSFERA bila je prilično drugačija.[31] To je bilo istraživanje bolesnika s kroničnim ZS zbog sistoličke disfunkcije lijeve klijetki uz povišene razine natrijuretskog peptida. Bolesnici su randomizirani za uzimanje aliskirena, enalaprila ili oba lijeka. Manji broj bolesnika imao je dijabetes (oko trećine), a bubrežna funkcija je bila znatno manje bila oštećena u bolesnika u istraživanju ATMOSPHERE nego kod onih u studiji ALTITUDE.[32] Rezultati istraživanja ATMOSPHERE bi trebali dati mnogo dublje razumijevanje moguće uloge aliskirena: svakako je moguće da bi mogao imati ulogu kao alternativa konvencionalnoj blokadi RAAS, a ne kao dodatak terapiji.

Antagonisti aldosterona

Problem ZS s normalnom ejekcijskom frakcijom (HeFNEF) ostaje i dalje enigma. Pokazao se kao entitet kojeg je klinički teško definirati unatoč prividnoj frekvenciji u epidemiološkim studijama, a klinička ispitivanja još uvijek nisu pokazala nikakvu uvjerljivu prednost bilo koje strategije liječenja. Drugo razočaranje je spironolakton. U bolesnika sa ZS zbog sistoličke disfunkcije lijeve klijetke nema sumnje da antagonisti mineralokortikoida poboljšavaju srčanu funkciju, simptome i preživljavanje.[33] Moglo bi se pomisliti da antagonisti mineralokortikoida vrlo vjerojatno djeluju u HeFNEF putem svojih antifibrotičkih svojstva. Međutim, u studiji Aldo-DHF provedenoj kod 422 bolesnika s HeFNEF, spironolakton nije imao utjecaj na poboljšanje kapaciteta fizičkog napora, simptome ili kvalitetu života.[34] Srednja vrijednost NT-proBNP u bolesnika uključenih u istraživanje iznosio je samo 158 ng/L što upućuje da je još jedno ispitivanje HeFNEF obuhvatilo bolesnike koji zaista nemaju ZS ili, ako imaju onda se radi o bolesnicima s istinski dobrom prognozom.

TERAPIJA UREĐAJIMA I PRAĆENJE

Telemonitoriranje

Postojao je znatan entuzijazam za primjenu telemonitoriranja, posebno kod onih koji vide ulogu ove metode kao način smanjenja bolničkog prijma među kroničnim bolesnicima. Uloga telemonitoriranja kod bolesnika sa ZS bila je predmetom debate. Iako su rane studije ukazale na to da bi mogao donijeti veliku korist, novija istraživanja su bila mnogo manje pozitivna, možda zato što se poboljšao osnovni standard skrbi bolesnika s kojima se uspoređivao telemonitoring.

Smatra se da ciljano intenzivno praćenje tijekom razdoblja visokog rizika, kao što je to odmah nakon bolničkog otpusta predstavlja najbolje korištenje telemonitoringa. U meta-analizi istraživanja uključujući više od 6.000 bolesnika, *Pandor i sur.*[35] su utvrdili da je telemonitoring nakon prijma u bolnicu bolesnika sa ZS bio povezan s boljim preživljavanjem, posebice tamo gdje je uobičajena skrb bila manje dobra.

Defibrilatori

Obično se misli da su okidanja implantabilnog kardioverter defibrilatora (ICD) bilo su indicirana ili to nisu, povezana s nepovoljnom prognozom kod bolesnika sa ZS.[36] Najčešći razlog za neprimjereno uključivanje ICD je fibrilacija atrija s

harmful. In the ASTRONAUT study,[29,30] 1,639 patients were randomised to aliskiren or placebo around 5 days after an index heart failure admission, again in addition to standard therapy. There was no effect on the main outcome measures of cardiovascular death or rehospitalisation with heart failure at 6 and 12 months, but a definite signal that aliskiren might be deleterious in patients with diabetes.

The ATMOSPHERE study[31] is rather different. It is a study of patients with chronic heart failure due to left ventricular systolic dysfunction and a raised natriuretic peptide level. Patients are randomised to aliskiren, enalapril or both. Fewer patients have diabetes (around a third), and renal function is considerably less impaired in patients in the ATMOSPHERE trial than in those in the ALTITUDE study.[32] The results of the ATMOSPHERE trial should give a much more profound understanding of the possible role of aliskiren: it is surely possible that it might have a role as an alternative to conventional RAAS blockade rather than as an add-on.

Aldosterone antagonists

The problem of heart failure with a normal ejection fraction (HeFNEF) remains tricky. It has proved a difficult entity to define clinically despite its apparent frequency in epidemiological studies, and no clinical trial has yet shown any convincing benefit from any treatment strategy. Another disappointment is spironolactone. In patients with heart failure due to left ventricular systolic dysfunction, there is no doubt that mineralocorticoid antagonists help improve cardiac function, symptoms and survival.[33] Mineralocorticoid antagonists might be thought to be particularly likely to work in HeFNEF through their anti?brotic properties. However, in the Aldo-DHF study conducted in 422 patients with HeFNEF, spironolactone had no effect on exercise capacity, symptoms or quality of life.[34] The mean N-terminal prohormone of brain natriuretic peptide level in the patients included in the study was only 158 ng/L, suggesting that yet again a trial of HeFNEF has included patients who really do not have heart failure or, if they do, they are patients with an intrinsically good prognosis.

DEVICE THERAPY AND MONITORING

Remote monitoring

There has been a great deal of enthusiasm for telemonitoring, particularly among commissioners who see it as a way of reducing admissions to hospital among patients with chronic disease. The role of remote monitoring for patients with heart failure has been much debated. Although early studies suggested that there might be a major bene?t, more recent trials have been much less positive, perhaps because the background standard of care against which telemonitoring is being compared has improved.

It might be that targeted intensive monitoring during periods of high risk, such as immediately after hospital discharge, makes the best use of remote monitoring. In a meta-analysis of trials involving over 6,000 patients, *Pandor et al*[35] found that remote monitoring following an admission with heart failure was associated with improved survival, particularly where usual care was less good.

Defibrillators

It is commonly thought that having discharges from an implantable cardioverter-defibrillator (ICD), whether appropria-

brzim ventrikulaskim odgovorom; osim toga, postaje sve očiglednije da se antitahikardijskom elektrostimulacijom može liječiti ventrikulska tahikardija bez potrebe za uključivanjem ICD. Istraživanje MADIT-RIT[37] je objavilo da se tehnikama programiranja kojima se povećava antitahikardijska elektrostimulacija i odgađa pražnjenje ICD smanjuje rizik od neprimjerenog pražnjenja. Došlo je do smanjenja ukupne smrtnosti za otprilike polovicu u grupi naprednog programiranja.

Zanimljivo, u kohortnoj studiji od 1.698 bolesnika, *Deyell i sur.*[38] nisu pronašli vezu između neprimjerenog okidanja ICD i nepovoljnog ishoda. Nasuprot tome, primjereno okidanje bio je povezano s HR od 3,11 za kombinirani završni cilj (smrt i transplantacij). Razlozi za nerazmjer nisu jasni: može biti povezano s činjenicom da su bolesnici u studiji *Deyell i sur*. bili manje simptomatski i vjerojatno bili na terapiji beta-blokatorima. Međutim, bez obzira na prognostičke implikacije, smanjujući neprimjerene okidanje, napredno programiranje ICD poboljšava kvalitetu života bolesnika smanjujući rizik od vrlo neugodnog okidanja ICD.

Srčana resinhronizacijska terapija

Drugi veliki uređaj za ZS predstavlja resinkronizacijska terapija elektrostimulatorom (CRT). Iako je dokazano da CRT povećava životni vijek u bolesnika sa ZS zbog sistoličke disfunkcije lijeve klijetke koji su u sinusnom ritmu i imaju blok lijeve grane i dalje su prisutne kontroverze. Mnogi su uvjereni da bolesnici s fibrilacijom atrija ili drugim oblicima smetnji provođenja mogu imati dobrobit od ovog liječenja, mada nema dokaza iz randomiziranih istraživanja koji bi to utvrdili.[39,40] Posebna tema koja se ponavlja je pojam 'odgovor': kod oko trećine bolesnika nema reakcije na primjenu CRT bilo zbog njihovih simptoma ili pojedinih ehokardiografskih indeksa funkcije lijeve klijetke. Stoga se smatra da vjerojatno postoje bolesnici s konvencionalnom indikacijom za CRT kojima bi se trebalo uskratiti liječenje CRT, dok bi drugi bez klasične indikacije mogli imati koristi zahvaljujući tzv. disinkroniji preoperativno.

Kako Witte ističe[41], deaktiviranje CRT uređaja u osoba koje ne reagiraju na ovu terapiju dovodi do hemodinamskog pogoršanja.[42] Definiranje odgovora na CRT u smislu promjene simptoma, ili lošije surogatnom varijablom poput volumena lijeve klijetke nije dobro jer ne možemo znati što bi se inače dogodilo bolesniku bez uređaja. Zanimljiva nova informacija je da se izgleda javlja inverzni odnos između trajanja simptoma ZS prije implantacije CRT i posljedičnog preživljavanja, posebice u osoba s abnormalnom bubrežnom funkcijom.[43] Ovo otkriće je zasigurno očekivano: što ranije u prirodnoj razvoju bolesti interveniramo, veća je vjerojatnost učinka. Međutim, ističe se potreba za razmišljanjem o implantiranju CRT kod bolesnika s manje teškim simptomima, ako imaju blok lijeve grane,[44] umjesto da se čeka dok bolesnicima ne postane lošije, ali moguće je da tada manja dobrobit.

Daljnji poticaj za raniju CRT implantaciju dolazi iz studije BLOCK-HF u kojoj su proučavani bolesnici s oštećenom sistoličkom funkcijom lijeve klijetke kao i konvencionalnom indikacijom za elektrostimulaciju u obliku atrioventrikulskog bloka.[45] Svim bolesnicima bio je ugrađen CRT uređaj, ali su bili kasnije randomizirani za konvencionalnu dvokomorsku elektrostimulaciju ili biventrikularnu elektrostimulaciju. Gotovo 700 bolesnika je bilo uključeno, a prosječna ejekcijska frakcija lijeve klijetke je bila 40%. Nitko nije imao konvencionalnu indikaciju za CRT. Ovo liječenje aktivnim CRT elektro-

te or inappropriate, is associated with an adverse prognosis in patients with heart failure.[36] The commonest reason for an inappropriate shock is atrial fibrillation with a rapid ventricular response; additionally, it is becoming increasingly apparent that antitachycardia pacing may treat ventricular tachycardia without a shock being necessary. The MADIT-RIT trial[37] reported that programming techniques that both increase antitachycardia pacing and delay ICD discharges reduce the risk of inappropriate discharge. There was a reduction in all-cause mortality of around a half in the advanced programming group.

Intriguingly, in a cohort study of 1,698 patients, *Deyell et al*[38] found no association between inappropriate ICD shock and an adverse outcome. In contrast, an appropriate shock was associated with a HR of 3.11 for the combined endpoint of death and transplantation. The reasons for the discrepancy are not clear: it may be related to the fact that the patients in *Deyell et al*'s cohort were less severely symptomatic and were more likely to be on beta-blocker therapy. However, regardless of the prognostic implications, by reducing inappropriate shocks, advanced programming of ICDs improves patients' quality of life by reducing the risk of a very unpleasant ICD discharge.

Cardiac resynchronisation therapy

The other major device for heart failure is, of course, the cardiac synchronisation therapy (CRT) pacemaker. Although it has been proved to increase life expectancy in patients with heart failure due to left ventricular systolic dysfunction, sinus rhythm and left bundle branch block, controversies remain. Many are convinced that patients in atrial fibrillation or other forms of conduction defect might benefit, although there is no evidence from randomised trials to support these beliefs.[39,40] A particular recurring theme is the concept of 'response': around a third of patients are said not to respond to CRT based on either their symptom status or some echocardiographic index of left ventricular function. The subtext is that there might be some patients with conventional indications for CRT who perhaps should be denied the treatment, and others with no indication who might benefit based on some measure of so-called dyssynchrony preoperatively.

As Witte points out,[41] deactivating a CRT device in a supposed 'non-responder' results in haemodynamic worsening.[42] Defining 'response' in terms of symptomatic change, or worse, a surrogate measure such as left ventricular volume, is doomed to fail — we cannot know what would otherwise have happened to the patient without the device. One interesting new piece of information is that there appears to be an inverse relation between the duration of heart failure symptoms prior to CRT implantation and subsequent survival, particularly in those with abnormal renal function.[43] This finding is surely expected: the earlier in the natural history of illness we intervene, the greater is the likely effect. However, it does highlight the need to think about implanting CRT in patients with less severe symptoms if they have left bundle branch block,[44] rather than waiting until patients are worse but may have less to gain.

Further encouragement for earlier CRT implantation comes from the BLOCK-HF study in which patients with impaired left ventricular systolic function and a conventional indication for pacing in the shape of atrioventricular block were studied.[45] All the patients had a CRT device implanted, but they were randomised later to conventional dual chamber pacing or biventricular pacing. Nearly 700 patients were in-

stimulatorom rezultiralo je smanjenjem u primarnom zajedničkom cilju, odnosno smanjenju smrtnosti od svih uzroka, hitnoj skrbi vezanoj za ZS ili >15% povećanjem krajnjeg sistoličkog volumena lijeve klijetke.

Vagalna stimulacija

Fascinantan novi uređaj za bolesnike s kroničnim ZS je vagalni stimulator, koji bi se potencijalno mogao kombinirati s postojećim uređajima.[46] Bolesnici s kroničnim ZS obično imaju neravnotežu između svoje pojačane aktivnosti simpatičkog živčanog sustava i smanjenje parasimpatičke aktivnosti. Vagalni stimulator isporučuje električnu stimulaciju vagalnom živcu u vratu povezanu sa srčanim ciklusom. Preliminarni podaci upućuju da bi mogao imati nekog učinka na kapacitet fizičkog napora, kvalitetu života i funkciju lijeve klijetke.[47] Studija od 650 bolesnika je trenutno u fazi izradi radi procjene djelovanja na ukupni mortalitet i hospitalizacije zbog ZS.[48]

TERMINALNO ZATAJIVANJE SRCA

Za bolesnike s terminalnim ZS postoje kontroverze o tome trebaju li se koristiti implantibilni defibrilatori. U britanskim smjernicama za upućivanje na transplantaciju srca[49] rješava se pitanje uporabe implantibilnog defibrilatora prema smjernicama NICE te se ističe da nemamo puno informacija za zbrinjavanje pacijenta bez ishemijske bolesti srca. Međutim, bolesnici na listama čekanja za transplantaciju srca imaju visok rizik od iznenadne smrti. U retrospektivnoj opservacijskog studiji s više od 1.000 bolesnika koji su bili na listi za potencijalnu transplantaciju srca, *Frülich i sur.* su otkrili značajnu dobrobit preživljavanja za bolesnike koji su dobili ICD u primarnoj prevenciji, neovisno o etiologiji ZS — tek oko jedne trećine bolesnika je imalo ishemijsku bolest srca.[50] Učinak je bio manje značajan za bolesnike kojima je indiciran ICD u sekundarnoj prevenciju. Možda ICD treba uzeti u obzir i šire kod bolesnika na listi čekanja za transplantaciju.

Neke stanice iz skupine uzoraka biopsije miokarda zajedno formiraju kardiosfere koje se potencijalno mogu diferencirati u mnogo vrsta stanica. U vrlo maloj studiji radi demonstriranja sigurnosti, bolesnici liječeni intrakoronarnim stanicama izvedenim iz kardiosfere (CDCS) nakon infarkta miokarda su imali manje volumene ožiljka i veće volumene mase srca od onih koji liječeni na standardan način.[51] CDC spadaju u dugačak popis potencijalnih izvora matičnih stanica, a niti jedna od njih u stvarnosti nije urodila plodom unatoč ogromnom entuzijazmu.

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cluded, and the average left ventricular ejection fraction was as high as 40%. None had a conventional indication for CRT. Those receiving active CRT pacing had a reduction in the primary endpoint of all-cause mortality, heart failure-related urgent care or a >15% increase in left ventricular end-systolic volume.

Vagal stimulation

A fascinating new device for patients with chronic heart failure is the vagal stimulator, which might potentially be combined with existing devices.[46] Patients with chronic heart failure commonly have an imbalance between their enhanced sympathetic nervous system activity and a decline in parasympathetic activity. The vagal stimulator delivers electrical stimulation to the vagus nerve in the neck, timed to the cardiac cycle. Preliminary work suggested that it might have some effect on exercise capacity and quality of life and left ventricular function.[47] A study of 650 patients is being mounted to assess its effects on all-cause mortality and hospitalisation for heart failure.[48]

END-STAGE HEART FAILURE

For patients with end-stage heart failure, there has been some controversy as to whether implantable defibrillators should be used. The UK guidelines on referral for heart transplantation[49] address the issue of use of implantable defibrillators in terms of NICE guidance, and point out that we do not have much information to guide the management of those without ischaemic heart disease. However, patients on cardiac transplant waiting lists are at high risk of sudden death, and in a retrospective observational study of over 1,000 patients listed for potential cardiac transplantation, *Frülich et al* found a marked survival benefit for patients receiving an ICD for primary prevention independent of the aetiology of heart failure — only around one-third of the patients had ischaemic heart disease.[50] The effect was very much less marked for patients receiving an ICD for secondary prevention. Maybe ICDs should be considered more widely in patients on a transplant waiting list.

Some cells from myocardial biopsy samples cluster together to form cardio spheres which can potentially differentiate into many cell types. In a very small study to demonstrate safety, patients treated with intracoronary cardiosphere-derived cells (CDCs) following myocardial infarction had smaller volumes of scar and larger volumes of viable heart mass than those receiving standard care.[51] CDCs join a long list of potential sources of stem cells, none of which has really borne fruit despite enormous enthusiasm.

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