Almanah 2014.: kardiomiopatije

Almanac 2014: Cardiomyopathies

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SAŽETAK: Kardiomiopatije su bolesti miokarda koje se ne mogu objasniti abnormalnim uvjetima punjenja niti promjenama koronarnih arterija. One se klasificiraju u više morfoloških i funkcionalnih fenotipova čiji uzrok mogu biti genetički i negenetički mehanizmi. Dominantne teme u radovima objavljenima u razdoblju 2012.-2013. slične su onima navedenima u Almanahu 2011.: uporaba (i interpretacija) genetskog testiranja, razvoj i primjena novih neinvazivnih tehnika slikovne dijagnostike te uporaba serumskih biomarkera u procesu dijagnoze i za prognozu. Važna inovacija od posljednjeg Almanaha jest razvoj sofisticiranijih modela za predviđanje neželjenih kliničkih događaja.

SUMMARY: Cardiomyopathies are myocardial disorders that are not explained by abnormal loading conditions and coronary artery disease. They are classified into a number of morphological and functional phenotypes that can be caused by genetic and non-genetic mechanisms. The dominant themes in papers published in 2012–2013 are similar to those reported in Almanac 2011, namely, the use (and interpretation) of genetic testing, development and application of novel non-invasive imaging techniques and use of serum biomarkers for diagnosis and prognosis. An important innovation since the last Almanac is the development of more sophisticated models for predicting adverse clinical events.

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UVOD

Kardiomiopatije su bolesti miokarda koje se ne mogu objasniti abnormalnim uvjetima punjenja niti promjenama koronarnih arterija. One se klasificiraju u više morfoloških i funkcionalnih fenotipova čiji uzrok mogu biti genetički i negenetički mehanizmi. Dominantne teme u radovima objavljenima u razdoblju od 2012. do 2013. godine su slične onima navedenima u Almanahu 2011., to jest uporaba (i interpretacija) genetičkog testiranja, razvoj i primjena novih neinvazivnih tehnika slikovne dijagnostike te uporaba serumskih biomarkera za dijagnozu i i prognozu. Važna inovacija od posljednjeg Almanaha jest razvoj sofisticiranijih načina predviđanja neželjenih kliničkih događaja.

INTRODUCTION

Cardiomyopathies are myocardial disorders that are not explained by abnormal loading conditions and coronary artery disease. They are classified into a number of morphological and functional phenotypes that can be caused by genetic and non-genetic mechanisms. The dominant themes in papers published in 2012–2013 are similar to those reported in Almanac 2011, namely, the use (and interpretation) of genetic testing, development and application of novel non-invasive imaging techniques and use of serum biomarkers for diagnosis and prognosis. An important innovation since the last Almanac is the development of more sophisticated models for predicting adverse clinical events.

HIPERTROFIJSKA KARDIOMIOPATIJA

Kardiološka slikovna dijagnostika i cirkulirajući biomarkeri

Hipertrofijska kardiomiopatija (HCM) javlja se u jedne od 500 odraslih osoba i kod većine je osoba naslijeđena kao autosomna domimantna karakteristika uzrokovana mutacijom gena sarkomernih proteina te je povezana s povećanim rizikom iznenadne srčane smrti (SCD), progresivnom disfunkcijom klijetki i moždanim udarom **(slika 1)**.[1-3] Dijagnostička sredstva poput EKG-a i ehokardiografije i dalje su osnovni načini dijagnoze i liječenja HCM-a, ali kardiološki MRI (CMR, od engl. *cardiac magnetic resonance*) pospješuje dijagnostičku točnost i pruža dodatne fenotipske informacije kod pacijenata s utvrđenom bolesti **(slika 2)**.[4-7] Na primjer, u jednoj studiji CMR je identificirao hipertrofiju u otprilike 10% nosilaca mutacije sarkomera kod kojih je ehokardiografija pokazala normalnu debljinu stijenke.[8] Novije CMR sekvencije, poput T1 mapiranja, pružaju kvantitativne procjene volumena ekstracelularnog miokarda (ECV) (i prema tome nadomjesno mjerenje intersticijske fibroze)[5]. Jedno je istraživanje pokazalo povećanje ECV kod osoba s mutacijama sarkomera, ali bez LV hipertrofije.[9] Ti rezultati ukazuju na to da selektivna uporaba CMR može biti korisna kod obiteljskih pregleda, pogotovo kada su ostala obilježja dosljedna sa HCM-om, poput ECG-abnormalnosti.

Klinička važnost ožiljka miokarda u abnormalnom nalazu kardiološkog MRI uz primjenu gadolinija tema je koja se često ponavlja u literaturi. Dostupni podatci ukazuju na povezanost između kasnog pojačanja gadolinijumom (LGE), koji predstavlja makroskopski fokalni ožiljak miokarda, i kardiovaskularne smrtnosti – smrti uzrokovane zatajivanjem srca i ukupne smrtnosti; no pokazuju samo trend k povećanju rizika od SCD.[10,11] ECV mjeren CMR-om pokazuje korelaciju s koncentracijom NT-proBNP (N-terminalni dio proBNP peptida) i serumskih biomarkera sinteze kolagena te pruža dodatne dokaze da je fibroza miokarda važna u ranoj patogenezi.[9]

Brojni su radovi istraživali biomarkere kao sredstva dijagnoze i prognoze i pokazali su predviđanja loših ishoda kod pacijenata sa zatajivanjem srca.[12] U istraživanju koje je uključilo 772 pacijenta sa HCM-om, moždani natriuretski peptid (BNP) bio je neovisan predskazatelj pobola i smrtnosti.[13] U drugom istraživanju s uključenih 183 ambulantnih pacijenata vrijednost plazmatskog NT-proBNP bila je prediktor događaja povezanih sa zatajivanjem srca[14] te prediktor smrtnih ishoda povezanih sa zatajivanjem srca i transplantacijom, ali ne i iznenadne smrti ili neprimjerenih šokova kardioverter-defibrilatora (ICD).[15] Daljnje istraživanje na 183 pacijenta pokazalo je povećane koncentracije seruma visoko osjetljivog troponina T te predvidjelo nepovoljne rezultate kod HCM.[16]

Strategije liječenja

Današnje liječenje osoba sa HCM-om usredotočuje se na prevenciju SCD i moždanih udara, nestanak simptoma opstrukcije izlaznog dijela lijeve klijetke refraktornih na lijekove i palijacijom ograničavajućih simptoma uzrokovanih sistoličkom ili dijastoličkom disfunkcijom. Od posljednjeg Almanaha napredak nije značajan, no rana profilaktička primjena

HYPERTROPHIC CARDIOMYOPATHY

Cardiac imaging and circulating biomarkers

Hypertrophic cardiomyopathy (HCM) occurs in one in every 500 adults and in most individuals is inherited as an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes and is associated with an increased risk of sudden cardiac death (SCD), progressive ventricular dysfunction and stroke **(Figure 1)**.[1–3] Diagnostic tools such as ECG and echocardiography remain fundamental to diagnosis and treatment of HCM but cardiac MRI (CMR) improves diagnostic accuracy and provides additional phenotypic information in patients with established disease **(Figure 2)**.[4–7] For example, in one study, CMR identified hypertrophy in about 10% of sarcomere mutation carriers thought to have normal wall thickness by echocardiography.[8] Novel CMR sequences, such as T1 mapping, provide quantitative estimates of the myocardial extracellular volume (ECV) (and therefore a surrogate measure of interstitial fibrosis)[5] and, in one study, an increase in ECV was reported in individuals with sarcomere mutations but without LV hypertrophy.[9] These findings suggest that selective use of CMR may be helpful in family screening, particularly when they are other features consistent with HCM, such as ECG abnormalities.

The clinical relevance of myocardial scar inferred from abnormal gadolinium enhanced CMR is a recurring subject in the literature. Available data support a relation among late gadolinium enhancement (LGE), representing macroscopic focal myocardial scar, and cardiovascular mortality, heart failure death and all-cause mortality but show only a trend towards an increased risk of SCD.[10,11] ECV measured by CMR correlates with concentrations of both N-terminal pro-brain natriuretic peptide and serum biomarkers of collagen synthesis providing further evidence that myocardial fibrosis is important early in disease pathogenesis.[9]

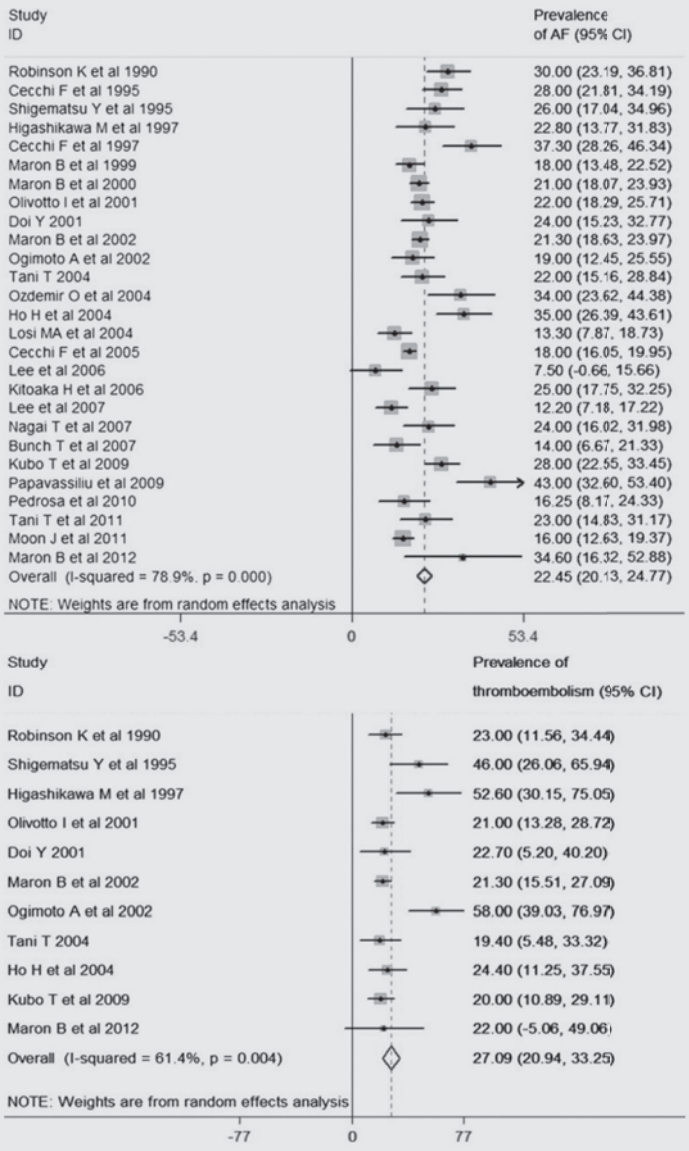
Numerous papers have investigated biomarkers as a tool for diagnosis and prognosis and have shown predicting poor outcome in patients with heart failure.[12] In a study of 772 patients with HCM, brain natriuretic peptide (BNP) was an independent predictor of morbidity and mortality.[13] In another study of 183 stable outpatients, plasma NT-proBNP was a predictor of heart failure-related events[14] and was a predictor of heart failure and transplant-related death but not sudden death or inappropriate implantable cardioverter defibrillator (ICD) shocks.[15] A further study of 183 patients reports elevated serum concentrations of high-sensitivity cardiac troponin T to predict adverse outcomes in HCM.[16]

Treatment strategies

Current management of individuals with HCM focuses on prevention of SCD and stroke, relief of drug-refractory symptoms associated with LV outflow tract obstruction (LVOTO), and palliation of limiting symptoms caused by systolic or diastolic dysfunction. There have been few developments in therapy since the last Almanac, but early prophylactic β-blocker therapy in physically active patients (NYHA 1 and 2) with provokable LVOTO has been shown to be effective in reduc-

FIGURE 1.

Prevalence of atrial fibrillation and thromboembolism. Guttmann *et al*[3] investigated a population of 7381 patients with hypertrophic cardiomyopathy. A meta-analysis reveals an overall prevalence of atrial fibrillation of 22.45%. The forest plot from random effect meta-analysis shows study-specific prevalence and the pooled (overall) prevalence of AF. The heterogeneity between the study was estimated as I2=78.9% (p<0.001). The overall prevalence of thromboembolism is 27.09%. The forest plot from random effect meta-analysis shows study-specific prevalence and the pooled (overall) prevalence of thromboembolism in patients with hypertrophic cardiomyopathy and atrial fibrillation. The heterogeneity between the studies was estimated as I2=61.4% (p<0.01).



beta-blokatora kod tjelesno aktivnih pacijenata (NYHA 1 i 2) s dinamičkim LVOTO pokazala se kao uspješna u smanjenju gradijenta tijekom fiziološkog vježbanja.[17] Druga je studija registrirala dobrobit disopiramida u terapiji simptomatskih pacijenata s opstrukcijom rezistentnom na primijenjen beta-blokator ili verapamil.[18]

Invazivno liječenje LVOTO preporučuje se pacijentima sa simptomima otpornosti na lijekove. Više studija je pružilo nove podatke o septalnoj ablaciji alkoholom (SAA) i septalnoj miektomiji LV. Tijekom 5,7 godina nakon zahvata, preživljavanje nakon SAA kod 177 pacijenata bilo je slično onom kod pacijenata sa septalnom miektomijom i sličnom kontrolnom skupinom. Srčani stimulatori bili su potrebni za 20,3% pacijenata koji su podvrgnuti SAA u usporedbi sa 2,3% u skupini operiranih tijekom 30 dana nakon zahvata.[19] Slični rezultating outflow gradients during physiological exercise.[17] Another study has confirmed the additive benefit of disopyramide in therapy of symptomatic patients with obstruction resistant to initial therapy with β-blocker or verapamil.[18]

Invasive treatment of LVOTO is recommended for patients with drug-refractory symptoms. Several studies have provided new data on septal alcohol ablation (SAA) and LV septal myectomy. Over a follow-up of 5.7 years, survival following SAA in 177 patients was similar to that of patients treated with septal myectomy and a matched control population. Pacemakers were required in 20.3% in patients who underwent SAA compared with 2.3% in the surgical cohort in the 30 days following the procedure.[19] Similar results following SAA were reported in a study of 470 patients[20] in whom 10-year survival (all-cause death rate 1.2%) was 88% compared

ti nakon SAA zabilježeni su u studiji na 470 pacijenata[20] kod kojih je 10-godišnja stopa preživljavanja (stopa ukupne smrtnosti 1,2%) bila 88% u usporedbi sa 84% u sličnoj normalnoj populaciji **(slika 3)**; isti autori također su zabilježili smanjenje SCD faktora rizika. U studiji na 239 pacijenata, septalna miektomija je također povezana sa smanjenjem učestalosti i povećanom stopom preživljavanja.[21] Druga studija iznosi kumulativnu učestalost smrti povezane sa HCM-om od 3,3% u 5 godina.[22] Naposlijetku, u 699 pacijenata su dob i perzistentna fibrilacija atrija iznešene kao predznak lošijeg ishoda kod pacijenata koji su podvrgnuti kirurškoj miektomiji.[23]

Novi podatci dovode u pitanje učinkovitost dvokomorne elektrostimulacije za refraktornu simptomatsku LVOTO.[24,25] U nedavnom Cochrane pregledu iznešeno je da svi podatci proizlaze iz malenih studija te da se nekoliko nasumičnih ispitivanja[26,27] koncentrira na mjerenja fizioloških ishoda a ne na čvrste kliničke ishode, pa stoga preporučuju velika i visoko kvalitetna ispitivanja.[28]

Prevencija iznenadne srčane smrti

Noviji sustavni pregled i meta-analiza 27 studija zabilježili su primjerenu stopu ICD intervencija od 3,3% na godinu s neprimjerenom stopom šoka od 4,8% godišnje[29], ali u studiji u jednom centru na 334 pacijenta sa HCM-om pacijenti su i dalje imali znatnu kardiovaskularnu smrtnost (pretežno uslijed srčanog zatajivanja) i iskusili česte neprimjerene šokove i komplikacije. Ovi nalazi sugeriraju da su potrebne nove strategije da bi se poboljšao odabir pacijenata za ICD i spriječio napredak bolesti kod onih koji su primili napravu **(slika 4)**.[30]

Suvremene procjene rizika ovise o malom broju lako dostupnih markera rizika za predviđanje SCD i često se koriste kao vodič pri ugradnji ICD-ova,[31,32] ali noviji dokazi ukazuju da je djelotvornost tog pristupa ograničena u razlikovanju osoba visokog i niskog rizika.[33] Uz to, više nedavno predloženih prognostičkih faktora (poput LVOTO i dobi) nisu uključeni u ovu procjenu.[10,32-34] Noviji podatci također su učvrstili važnost dobi pri stratifikaciji rizika. U istraživanju od 428 pacijenata dobi iznad 60 godina, 3,7% ih je umrlo od sekundarnih uzroka povezanih sa HCM koji uključuju embolijski moždani udar, zatajivanje srca i transplantaciju. Iznenadna srčana smrt je reistrirana kod 5 pacijenata (1,2% ili 0,2% godišnje). Autori zaključuju da su pacijenti sa HCM stariji od 60 godna manje podložni riziku smrti povezane sa HCM-om ili nagle smrti.[35]

Predloženo je da se konvencionalni algoritmi za predviđanje stope rizičnosti ne primjenjuju na pedijatrijsku populaciju.[36] U pedijatrijskoj skupini za koju je klinički procijenjeno da je visokorizična, primjereni šokovi ICD-a zbili su se kod 10% od 224 pacijenta nakon praćenja od 4,3 ± 3,3 godina, s godišnjom stopom od 4,5%. Međutim, kako su se komplikacije vezane za medicinske uređaje dogodile u 41% pacijenata (pogotovo komplikacije elektrode i neprimjereni impulsi),[37] potrebno je više podataka za pedijatrijske skupine da bi se procijenila isplativost ICD terapije kod mladih.

Isplativost obiteljskog probira

Ekonomski modeli genskog testiranja za evaluaciju obitelji sa HCM-om pokazuju da su genetska testiranja isplativa kada se kombiniraju s konvencionalnim kliničkim testiranjima.[38,39] Ti

with 84% in a matched normal population **(Figure 3)**; the same authors also report a reduction in SCD risk factors. In a study of 239 patients, septal myectomy was associated with a reduction in syncope and increased survival.[21] Another study reports a cumulative incidence of HCM-related death of 3.3% at 5 years.[22] Finally, in 699 patients age and persistent atrial fibrillation were reported to be predictors of poorer outcome in patients undergoing surgical myectomy.[23]

New data have re-examined the efficacy of dual chamber pacing for refractory symptomatic LVOTO.[24,25] In a recent Cochrane review, it was noted that all data derive from small studies and that the few randomised trials[26,27] concentrate on physiological outcome measures rather than hard clinical endpoints. As a result, they recommend large and high quality trials.[28]

Prevention of SCD

A recent systematic review and meta-analysis of 27 studies reported an appropriate ICD intervention rate of 3.3% per year with an inappropriate shock rate of 4.8% per annum[29] but in a single centre study of 334 patients with HCM, patients still had a significant cardiovascular mortality (predominantly heart failure) and experienced frequent inappropriate shocks and implant complications. These findings suggest that new strategies are required to improve patient selection for ICDs and prevent disease progression in those who receive a device **(Figure 4)**.[30]

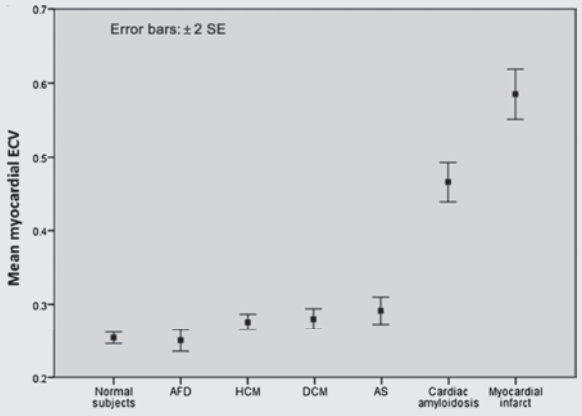
Contemporary risk assessment relies on a small number of readily obtained clinical risk markers to predict SCD and is widely used to guide implantation of ICDs,[31,32] but recent evidence suggests that this approach distinguishes high and low risk individuals with only limited predictive power.[33] Additionally, several recently proposed prognostic factors (such as LVOTO and age) are not included in the assessment.[10,32-34] Recent data have also reinforced the importance of age in risk stratification. In a study of 428 patients above the age of 60 years, 3.7% died secondary to HCM-related causes including embolic stroke, heart failure and transplantation. SCD events occurred in five patients (1.2% or 0.2% per year). The authors conclude that patients with HCM surviving to an age above 60 are at low risk for HCM-related mortality and sudden death.[35]

It has been suggested that conventional risk prediction algorithms do not apply to paediatric populations.[36] In a paediatric cohort, judged clinically to be at high risk, appropriate ICD shocks were delivered in 19% of 224 patients followed for 4.3 ± 3.3 years with an annual rate of 4.5% per year. However, as device-related complications occurred in 41% (especially lead complications and inappropriate shocks) of patients,[37] more data in paediatric cohorts are required to determine the net benefit of ICD therapy in the young.

Cost efficacy of family screening

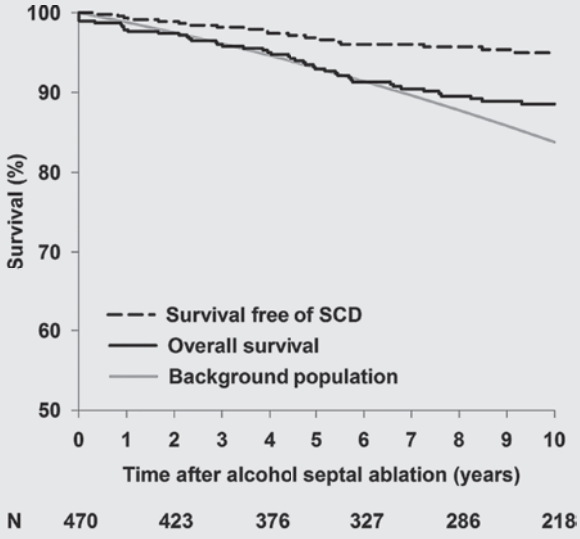
Economic models of genetic testing for the evaluation of families with HCM report that genetic testing is cost-effective when combined with conventional clinical screening.[38,39] These models are based on the assumption that risk-algorithms from high risk populations can be applied to low risk populations detected through screening and that preventive

FIGURE 2



Extracellular volume (ECV) in health and disease: inter-group comparison showing disease-specific variability. Sado *et al*[5] measured and assessed the significance of myocardial ECV as a clinical biomarker in health and a number of cardiac diseases. The data are presented as mean±2 SEs.

FIGURE 3.



Jensen *et al*[20] investigated overall survival (solid black) and survival free of sudden cardiac death (SCD) including appropriate implantable cardioverter defibrillator discharge and aborted cardiac arrest (dashed black) after alcohol septal ablation in 470 patients with hypertrophic obstructive cardiomyopathy (follow-up 8.4±4 years). Comparison is made with the overall survival of an age- and sex-matched background population (grey). N indicates number of patients at risk at the indicated time.

se modeli zasnivaju na pretpostavkama da se algoritmi rizika iz visokorizičnih populacija mogu primijeniti na niskorizične populacije otkrivene putem testiranja te da je preventivno liječenje ICD-ima učinkovito. Pored toga, ovi modeli i mnogi programi kliničkih testiranja pretpostavljaju relativno visoku prodornost bolesti.

U istraživanju koje je uspoređivalo klinička testiranja i prediktivna genetička testiranja kod djece i adolescenata, 90 pacijenata sa HCM-om i 361 član njihovih obitelji praćeni su tijekom 12 godina.[40] U grupi od 12 mladih nosilaca mutacije bez hipertrofije LV, pri prvobitnoj procjeni samo su dva razvila HCM tijekom perioda studije, što sugerira neočekivano nisku prodornost tijekom adolescencije, razdoblja koji se obično povezuje s najvećom stopom fenotipskih konverzija. Važno je naglasiti da su ta dva slučaja dijagnosticirana u dobi od 26 i 28 godina, što pokazuje važnost testiranja i nakon adolescencije. Uobičajene strategije kliničkog testiranja te klinička uloga genetičkog testiranja i njegova isplativost trebat će se ponovno evaluirati ako veća istraživanja pokažu slične rezultate.

Početni dokazi sugeriraju da dugotrajna klinička i genetička testiranja kod djece i odraslih nisu povezana s velikim nepovoljnim fiziološkim posljedicama.[40] Treba procijeniti učinak na društvene i profesionalne aspekte.

Povezanost genotipa s fenotipom

Uspostava klinički korisnih veza između genotipa i fenotipa i dalje izostaje u HCM-u. Nedavni sistemski pregled pokazao je višu učestalost obiteljske prošlosti HCM-a i SCD-a, mlađu dob pojave i veći maksimalni LV kod osoba s mutacijom sarkomer gena, ali nikakva razlika nije zabilježena u kliničkim karakteristikama kad se uspoređuju MYBPC3 i MYH7 mutacije. Me-

treatment with ICDs is effective. Additionally, these models and many clinical screening programmes assume a relatively high disease penetrance.

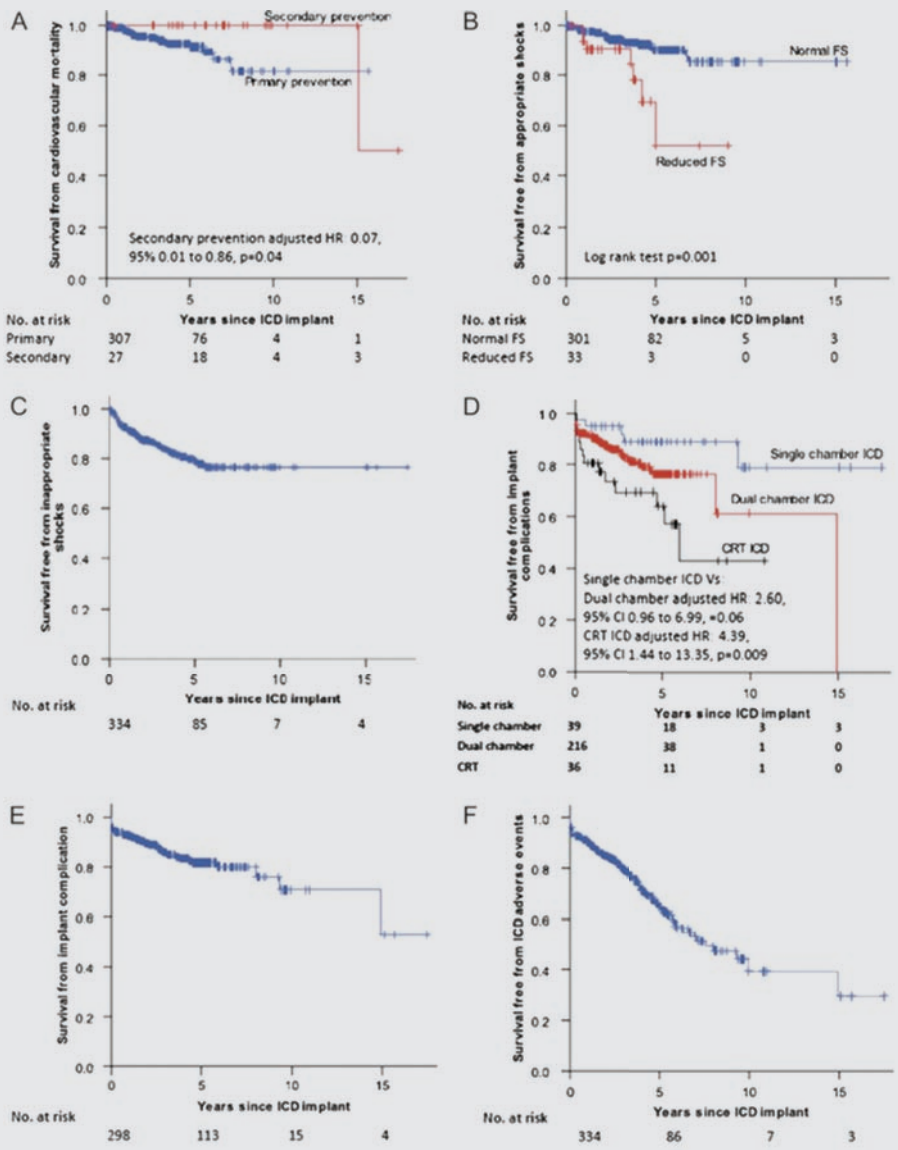
In a study comparing clinical screening and predictive genetic testing in children and adolescents, 90 patients with HCM and 361 relatives were followed for 12 years.[40] In a group of 12 young mutation carriers without LV hypertrophy, at initial assessment only two developed HCM during the period of the study suggesting an unexpectedly low penetrance during adolescence, a period conventionally associated with the greatest rates of phenotype conversion. Importantly, the two cases were diagnosed at the ages of 26 and 28 years, emphasising the importance of screening beyond adolescence. Conventional clinical screening strategies and the clinical role of genetic testing including its cost-effectiveness will need to be re-evaluated if larger studies show similar findings.

Preliminary evidence suggests that long term clinical and genetic screening in children and adults is not associated with major adverse psychological consequences.[40] The effect on social and professional aspects has to be evaluated.

Genotype–phenotype relations

The establishment of clinically useful relations between genotype and phenotype remains elusive in HCM. A recent

FIGURE 4.



O'Mahony *et al*[30] evaluated 334 patients with hypertrophic cardiomyopathy (HCM) at risk of sudden death treated with ICD. They conclude that HCM patients with an ICD have a significant cardiovascular mortality and are exposed to frequent inappropriate shocks and complications. Kaplan–Meier curves for survival free from cardiovascular mortality end-point (A) stratified according to device implantation for primary or secondary prevention, appropriate shocks (B) stratified according to impaired systolic function, inappropriate shocks (C), implant complications (D) stratified according to device complexity, implant complications in patients with singleor dual-chamber ICDs (cardiac resynchronisation therapy patients excluded) (E), and implantable cardioverter defibrillator-related adverse events (inappropriate shocks or implant complications) for the whole cohort (F).

đutim, ovi su podatci ograničeni nedosljednošću ustroja studije te malim brojem članova mnogih proučavanih skupina.[41]

Uz tradicionalne studije kliničke ekspresije, više istraživačkih skupina koristi ljudski inducirane kardiološke miocite izvedene iz pluripotentnih matičnih stanica (iPSC) da bi proučavali patogenezu bolesti. Imunobojenje i membransko uklještenje (eng. *patch clamping*) upotrijebljeni su da bi se identificirali fenotipi specifični za bolest i razlike u toksičnosti kardioloških lijekova među različitim linijama stanica.[42] Ista je skupina koristila slične tehnike da bi prikazala kako je ponovna uspostava homeostaze kalcija spriječila razvoj hipertrofije miocita i elektrofiziološke abnormalnosti kod kardiomiocita koji nose MYH7 mutaciju izvedenu iz pluripotentnih matičnih stanica.[43]

systematic review reported a higher prevalence of family history of HCM and SCD, younger age at presentation, and greater maximal LV in individuals with a sarcomere gene mutation but no difference was reported in clinical characteristics when comparing MYBPC3 and MYH7 mutations. However, these data were limited by the inconsistency of study design and the small size of many study cohorts.[41]

In addition to traditional clinical expression studies, several groups are using human induced pluripotent stem cell (iPSC)-derived cardiac myocytes to study disease pathogenesis. Immunostaining and patch clamping were used to identify disease-specific phenotypes and differences in cardiac drug toxicity between different cell-lines.[42] The same group used a similar technique to demonstrate that restoration of calcium homeostasis prevented the development of myo-

ARITMOGENA KARDIOMIOPATIJA DESNE KLIJETKE

Aritmogena kardiomiopatija desne klijetke (ARVC) klinički je obilježena aritmijom, SCD-om i progresivnim zatajivanjem srca. Gubitak kardiomiocita i njihova zamjena fibroznim ili fibro-masnim tkivom histološka su obilježja ove bolesti. ARVC je uzrokovana mutacijama u genima koji kodiraju sastavne elemente interkalacijskih diskova kardiomiocita kod velikog postotka pacijenata.[44] Dijagnoza zahtijeva integraciju podataka od članova obitelji, genetskog testiranja, elektrokardiografije i tehnika slikovne dijagnostike.[45] SCD i liječenje simptomatske aritmije i zatajivanja srca predstavljaju velik izazov liječenju bolesti.

Klinička dijagnoza ARVC

Iako dokazi ukazuju na to da su nedavne promjene predviđenih dijagnostičkih kriterija poboljšali dijagnostičku osjetljivost i specifičnost,[46,47] postoji zabrinutost da su oni i dalje ostali preosjetljivi u određenih skupina, poglavito sportaša i ljudi afričko-američkog etničkog podrijetla, gdje su mnoge strukturne i elektrografske promjene koje su normalne za ove grupe također i manji dijagnostički kriteriji za ARVC.[48,49]

Nove metode za otkrivanje ranih fenotipskih ekspresija ARVC uključuju imunohistokemijski i elektrofiziološki pristup. Prema jednom izvješću, imunohistokemijski pokazatelj redukcije signala plakoglobina u biopsijama miokarda ima osjetljivost od 85% i specifičnost od 57% za ARVC. Autori predlažu da se test može koristiti pri dijagnozi,[50] ali da izvedba pri analizi kod pred-fenotipskih slučajeva – gdje je i najkorisnija – nije bila testirana. Druga grupa istražitelja zamijetila je znatnu redukciju imunoreaktivnih signala za plakoglobin na sjecištima kardioloških miocita kod pacijenata sa sarkoidozom i miokarditisom velikih stanica.[51] To ukazuje na nove mehanizme oboljenja koji uključuju desmosomalne proteine u granulomatoznom miokarditisu i implicira citokinezu u dislokaciji plakoglobina iz dezosoma i u razvoju aritmije kod ARVC-a.

Nedavno istraživanje izvijestilo je o abnormalnostima u kinetici provodnosti-repolarizacije koja su otkrivena pomoću elektrofiziološkog testiranja 10 nepovezanih osoba i modela miša s mutacijom desmoplakina.[52] Važno je primijetiti da su ove abnormalnosti prethodile vidljivim strukturalnim promjenama.

Etiologija

ARVC se nasljeđuje kao autosomna dominantna karakteristika u gotovo 50% slučajeva[53] te normu predstavljaju nepotpuno prodiranje (uključujući prodiranje ovisno o dobi) i varirajuće kliničko izražavanje. Tijekom prethodne godine, genska heterogenost ARVC-a bila je istaknuta izvješćima o novim mutacijama u genima za fosfolamban, dezmokolin-2, TMEM43, CTNNA3 (α T katenin) i deleciji gena u plakofilinu-2.[54-60] Uz to, u obiteljima i u istraživanjima osoba sa ARVC-om primijećene su mutacije u genima koji su do tada povezivani s drugim kardiomiopatijama, a uključuju ne-dezmosmoalni protein lamin A/C.[61] Uloga drugih genetičkih i epigenetičkih mehacyte hypertrophy and electrophysiological abnormalities in pluripotent stem cell-derived cardiomyocytes carrying a MYH7 mutation.[43]

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is clinically characterised by arrhythmia, SCD and progressive heart failure. Cardiomyocyte loss and replacement by fibrous or fibrofatty tissue are histological hallmarks of the disease. ARVC is caused by mutations in genes that encode constituents of the intercalated disc of cardiomyocytes in a large proportion of patients.[44] Diagnosis requires integration of data from family members, genetic testing, electrocardiography and imaging techniques.[45] SCD and treatment of symptomatic arrhythmia and heart failure are the major management challenges.

Clinical diagnosis of ARVC

While evidence suggests that recent modification of proposed diagnostic criteria has improved diagnostic sensitivity and specificity, [46,47] there is a concern that they remain too sensitive in particular scenarios, most notably athletes and in people of black African ethnic origin, as many structural and electrographic changes considered normal in these groups are also minor diagnostic criteria for ARVC.[48,49]

Novel methods to detect early phenotypic expression in ARVC have included immunohistochemical and electrophysiological approaches. A report suggested that immunohistochemical demonstration of reduced plakoglobin signal in myocardial biopsies has a sensitivity of 85% and specificity of 57% for ARVC. The authors suggested the test could be used in diagnosis,[50] but the performance of the assay in prephenotypic cases—where it is most valuable — has not been assessed. Another group of investigators observed a marked reduction in immunoreactive signal for plakoglobin at cardiac myocyte junctions in patients with sarcoidosis and giant cell myocarditis.[51] This suggests new disease mechanisms involving desmosomal proteins in granulomatous myocarditis and implicates cytokines in dislocation of plakoglobin from desmosomes and in the development of arrhythmia in ARVC.

A recent study reported abnormalities in conductionrepolarisation kinetics detected by invasive electrophysiological testing in 10 unrelated individuals and a mouse model with desmoplakin mutations.[52] Notably, these abnormalities preceded overt structural changes.

Aetiology

ARVC is inherited as an autosomal dominant trait in up to 50% of cases[53] and incomplete penetrance (including age-dependent penetrance) and variable clinical expression are the norm. Over the last year, the genetic heterogeneity of ARVC has been underlined by reports of novel mutations in the genes for phospholamban, desmocollin-2, TMEM43, CTNNA3 (α T catenin) and a gene deletion in plakophilin-2.[54–60] Additionally, mutations in genes hitherto associated with other

nizama na izražavanje bolesti ostaje područje aktivnog istraživanja.[62]

Napredci u genetici mogli bi poboljšati specifičnost dijagnostičkih logaritama u budućnosti, ali podatci pokazuju da postoji mnogo izazova pri interpretaciji slijeda podataka. U istraživanju s 427 kontrolnih pacijenata i 93 ARVC probandi[63] sekvencirani su eksoni i akceptori cijepanja / donorska mjesta PKP2, DSP, DSG2, DSC2 i TMEM43. Moguće patogene mutacije identificirane su u 58% ARVC slučajeva, ali su također pronađene i kod 16% članova kontrolne skupine. Većina (43%) tih mutacija bile su radikalne (npr. mutacije mjesta cijepanja, besmislene mutacije, insercije ili delecije unutar okvira ili njegova pomaka) u usporedbi sa samo 0,5% kod kontrolnih pacijenata, ali učestalost mutacije pogrešnog čitanja je bila slična kod pacijenata (21%) i kontrola (16%). Važni nalazi bili su i viša učestalost kandidatskih varijanti, pogotovo mutacije pomaka, kod ne-bijelaca nego kod bijelaca u kontrolnoj skupini (19,44% i 5,83%) te slični brojevi varijanti u DSP, DSC2 i TMEM43 genima kod ARVC i kontrolne skupine. Ovi nalazi oprimjeruju konzervativni pristup kojim se mora služiti prilikom interpretacije genskih varijanti kod ARVC.

Uporaba iPSCa kao modela ARVC nedavno je opisana.[64] Kardiociti heterozigotno mutiranog plakofilin-2 iPSC pokazuju pretjeranu lipogenezu i apoptozu te je zabilježen deficit obrade kalcija kod homozigotnih mutanata. Bolje razumijevanje ovih fenomena moglo bi dovesti do razvoja novih terapijskih strategija koje bi mogle promijeniti liječenje u budućnosti.

Strategije zbrinjavanja

Jednom kada je ARVC dijagnosticiran, liječenje bi trebalo uključivati procjenu rizika SCD, indikacije za medikamentnu terapiju te promjene u načinu života. Iako se lijekovi za aritmiju poput amiodarona i sotalola često propisuju da bi se smanjio teret aritmije,[44] postoji malo dokaza da oni pospješuju preživljavanje ili mijenjaju tijek bolesti. Isto vrijedi i za liječenje bilo kojeg sistoličkog oštećenja funkcije LV pomoću ACE inhibitora i beta-blokatora.

Pokazano je da tjelesno vježbanje i natjecateljski sportovi dovode do povećanja rizika od iznenadne smrti[65,66] te se stoga ne preporučuju.[67,68] Nedavno je zabilježeno da je vježbanje povezano s povećanjem prodiranja bolesti i rizikom aritmije kod osoba s dezmosomalnom mutacijom. Kriteriji radne skupine bili su učestalije dostignuti tijekom razdoblja nakon zahvata, a simptomi su se pojavili u mlađoj dobi kod 56 sportaša koji su nosioci mutacije nego kod sjedilačkih nosilaca mutacije. Ovi su sportaši također imali smanjenu stopu preživljavanja bez ventrikularne tahikardije (VT)/ventrikularne fibrilacije i zatajivanja srca.[69] Ovi nalazi u korelaciji su s predkliničkim promatranjima mišjih modela ARVC s defektima gena plakofilina.[70]

Liječenje VT u ARVC pomoću kateterske ablacije povezuje se s visokom stopom ponovnog pojavljivanja,[71,72] ali nedavno multicentrično istraživanje usredotočeno na novije strategije ablacije proučavalo je ponovno pojavljivanje VT-a nakon radiofrekvencijske ablacije i utjecaj na teret VT-a. Autori su pronašli znatnu redukciju tereta VT-a i stopu dužeg preživljavanja bez VT-a nakon epikardijalne ablacije u usporedbi s endokardijalnim zahvatom. Međutim, stopa ponovnog pojav-

cardiomyopathies have been reported in families and studies of individuals with ARVC. These include the non-desmosomal protein lamin A/C.[61] The role of other genetic and epigenetic mechanisms on disease expression remains an area of active research.[62]

Advances in genetics may improve the specificity of diagnostic algorithms in the future but data show that there are many challenges in the interpretation of sequence data. In a study of 427 controls and 93 ARVC probands,[63] exons and splice acceptor/ donor sites of PKP2, DSP, DSG2, DSC2 and TMEM43 were sequenced. Likely pathogenic mutations were identified in 58% of the ARVC cases, but were also found in 16% of the controls. The majority (43%) of the candidate mutations in cases were radical (ie, splice site, nonsense, inframe and frame-shift insertions and deletions) compared with only 0.5% of controls but the frequency of missense mutations was similar in cases (21%) and controls (16%). Other important findings were a higher frequency of candidate variants, in particular missense, in non-Caucasian versus Caucasian controls (19.44% vs 5.83%) and similar numbers of variants in the DSP, DSC2 and TMEM43 genes in the ARVC and control groups. These findings illustrate the conservative approach that must be followed when interpreting genetic variants in ARVC.

The use of iPSCs as a model of ARVC was recently described.[64] Heterozygous mutant plakophilin-2 iPSC cardiomyocytes demonstrated exaggerated lipogenesis and apoptosis and calcium-handling deficits were detected in homozygous mutants. Greater understanding of these phenomena might lead to development of novel disease-modifying therapeutic strategies in the future.

Management strategies

Once ARVC has been diagnosed, management should include an assessment of SCD risk, indications for drug therapy and need for lifestyle changes. Although antiarrhythmic drugs such amiodarone and sotalol are frequently prescribed to decrease arrhythmic burden,[44] there is little evidence that these improve survival or alter the natural history of disease. The same is true for treatment of any associated LV systolic impairment with ACE inhibitors and β-blockers.

Physical exercise and competitive sport have been reported to increase the risk of sudden death[65,66] and are consequently not recommended.[67,68] More recently, exercise has been associated with increased disease penetrance and arrhythmic risk in individuals with a desmosomal mutation. Task force criteria were more likely to be met at follow-up and symptoms developed at a younger age in 56 endurance athletes carrying a mutation compared with more sedentary mutation carriers. These athletes also had a decreased lifetime survival free from ventricular tachycardia (VT)/ventricular fibrillation and heart failure.[69] These findings correlate with preclinical observations in murine model of ARVC with plakophilin gene defects.[70]

Catheter ablation to treat recurrent VT in ARVC has been associated with high recurrence rates[71,72] but a recent multicentre study with focus on newer ablation strategies assessed recurrence of VT following radiofrequency ablation and effect on burden of VT. The authors report a significant reduction in

ljivanja ostaje znatna sa sveukupnim izostankom VT od 47% tijekom prve godine.[73] Ovi podatci upućuju na to da kateterska ablacija može biti korisna za podgrupu pacijenata sa stalnim ili učestalim VT koji je otporan na terapiju lijekovima. Neki podatci sugeriraju da je VT koji se pripisuje lokaliziranoj bolesti moguća buduća indikacija.[74]

Sprječavanje iznenadne smrti

Trenutne AHA/ACC/ESC smjernice za zbrinjavanje pacijenata s ventrikularnim aritmijama i sprječavanje SCD-a preporučuju ICD implantaciju kod pacijenata s ARVC je kod kojih je zabilježen kontinuirani VT ili ventrikularna fibrilacija usprkos optimalnoj terapiji.[75] Noviji pregledni članak koji je istraživao rezultate i komplikacije ICD implantacija kod ARVC uključivao je 610 pacijenata. Tijekom praćenja od 3,8 godina, autori su zamijetili primjerene ICD intervencije u stopi od 9,5% godišnje s neprimjerenim intervencijama (3,7%) te komplikacijama koje su uključivale pogrešno funkcioniranje elektroda, pomicanje i infekciju (20,3% stope bilo koje komplikacije).[76] Ti rezultati upućuju na potrebu za zadovoljavajućom stratifikacijom rizika kako bi se smanjila smrtnost kao posljedica komplikacija povezanih s ICD-om. Važno je istaknuti da su pacijenti analizirani u spomenutom preglednom članku primili ICD za primarnu ili sekundarnu prevenciju. To bi u nekoj mejri moglo objasniti visoku stopu primjerenih intervencija.

Povećavajuća vrijednost i uloga CMR-a u stratifikaciji rizika proučena je u 69 pacijenata s mutacijama povezanima s ARVC-om (82% sa PKO-2 mutacijama) bez prethodno stalnog VT.[77] Električke abnormalnosti otkrivene su kod 61% pacijenata od kojih je 49% također imalo abnormalan nalaz CMR-a (definiran kao prisutnost barem manjeg broja kriterija radne skupine). Samo je jedan pacijent (4%) bez električkih abnormalnosti imao abnormalno srce na početnom oslikavanju. Tijekom razdoblja od 5,8 ± 4,4 godina, epizode stalnog VT dogodile su se samo kod pacijenata s abnormalnim nalazom elektrokardiograma i CMR-om. Autori su zaključili da među nosiocima mutacija prisutnost i električkih i CMR abnormalnosti ukazuje na pacijente visokog rizika. Slično istraživanje o prognozi za pacijente koji su pod promatranjem zbog ARVC-a iznosi pozitivne predviđene vrijednosti abnormalnog CMR-a kod 369 pacijenata koji ispunjaju barem jedan manji ili veći dijagnostički kriterij za ARVC. Negativne predviđene vrijednosti normalnog CMR-a su 98,8% za razdoblje od 4,3 ± 1,5 nakon liječenja.[78]

Potraga za biomarkerima koji dopuštaju ranu dijagnostiku i stratifikaciju rizika aktivno je polje istraživanja. Primjerice, niže koncentracije seruma prijemosnog integratora 1, proteina povezanog s membranama, povezuju se s ventrikularnim aritmijama i smanjenim statusom funkcioniranja u maloj skupini od 24 pacijenta sa ARVC-om.[79]

Novije strategije za predviđanje rizika u nositelja desmosomalnih mutacija povezanih sa ARVC-om predlažu uporabu evaluacije obiteljske anamneze, elektrokardiograma i nalaza 24-satnog holter EKG-a.[80] Fenotipske karakteristike koriste se za stratifikaciju rizika od stalnog VT-a. Istraživači su uključili 215 pacijenata tijekom razdoblja nakon zahvata u prosjeku od 7 godina. Rizičnost pacijenata stratificirana

VT burden and longer survival free of VT following epicardial ablation compared with an endocardial procedure. However, recurrence rates remain considerable with an overall freedom from VTof 47% at 1 year.[73] These data suggest that catheter ablation may be helpful in a subgroup of patients with incessant or frequent VT refractory tomedical therapy. Some data suggest that VT attributable to localised disease is a further potential indication.[74]

Prevention of sudden death

Current AHA/ACC/ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD recommend ICD implantation in patients with ARVC who have documented sustained VT or ventricular fibrillation and are receiving optimal medical treatment.[75] A recent literature review investigating outcomes and complications of ICD implantation in ARVC included 610 patients. During the 3.8-year follow-up, the authors reports appropriate ICD interventions at a rate of 9.5% per year with inappropriate interventions (3.7%) and complications including lead malfunction, displacement and infection (20.3% rate of any complication).[76] Once again, this underlines the need for appropriate risk stratification to minimise morbidity secondary to ICD-related complications. It is important to point out that the patients analysed in this review received an ICD for primary or secondary prevention. This could at least partially account for the high rate of appropriate interventions.

The incremental value and role of CMR in risk stratification were investigated in 69 patients with ARVC-associated mutations (83% with PKP-2 mutations) without prior sustained VT.[77] Electrical abnormalities were found in 61% of patients of whom 48% also had an abnormal CMR (defined as presence of at least a minor task force criterion). Only a single patient (4%) without electrical abnormalities had an abnormal heart on imaging at baseline. Over a period of 5.8±4.4 years, episodes of sustained VT only occurred in patients with ECG and CMR abnormalities. The authors concluded that among mutation carriers the presence of both electrical and CMR abnormalities identified high risk patients. A similar study on prognosis in patients under evaluation for ARVC reports a positive predictive value of an abnormal CMR in 369 patients who fulfilled at least one minor or major diagnostic criterion for ARVC. The negative predictive value of a normal CMR was 98.8% over a follow-up of 4.3±1.5 years.[78]

The search for biomarkers that allow early diagnosis and risk stratification is an active area of research. For example, low serum concentrations of Bridging integrator 1, a membrane-associated protein, were associated with ventricular arrhythmias and reduced functional status in a small cohort of 24 patients with ARVC.[79]

A novel strategy to risk prediction in ARVC-associated desmosomal mutation carriers proposes the use of pedigree evaluation, ECG and Holter information.[80] Phenotypic characteristics were used in stratifying the risk of sustained VT. The investigators included 215 patients over a mean follow-up of 7 years. Patients were risk stratified according to repolarisation and depolarisation abnormalities on ECG. Event-free survival

je po anomalijama repolarizacije i depolarizacije na elektokardiogramu. Preživljavanje bez novih epizoda tijekom 5 godina je bilo 33% u visokorizičnoj skupini naspram 97% u niskorizičnoj skupini.

DILATACIJSKA KARDIOMIOPATIJA

Dilatacijska kardiomiopatija (DCM) jedna je od najrašireniji bolesti miokarda u razvijenim zemljama. Definira se kao sistoličko oštećenje i proširenje LV-a bez prisutnosti prethodnog infarkta miokarda. Zadnjih je godina nekoliko istraživanja naglasilo značaj genetike u etiologiji naslijeđenih i prividno stečenih oblika DCM-a. Standarno liječenje zatajivanja srca temeljeno na simptomima i prognozi predstavlja glavni način liječenja, ali u zadnje vrijeme se više pažnje posvećuje važnosti etiologije u odabiru pristupa zbrinjavanju.

Genske podvrste dilatacijske kardiomiopatije

Više je istraživanja pročavalo prirodnu povijest DCM-a koji je uzrokovan mutacijama gena lamin A/C (LMNA). To se povezuje s poremećajem provođenja, atrijskom aritmijom, srčanim zatajivanjem i iznenadnom smrću te se treba na te mutacije posumnjati kada je DCM popraćen povišenom vrijednošću serumske kreatin-kinaze, poremećajima provođenja ili čestim aritmijama. Kod takvih pacijenata, dokazi ukazuju na to da treba uzeti u obzir ICD pri mnogo nižim razinama nego u drugim slučajevima DCM.[81-83] Multicentrična skupina od 269 pacijenata s LMNA mutacijom otkrila je netrajnim VT, LVEF <45%, muški spol i nepostojanje mutacije pogrešnog čitanja kao rizične čimbenike za maligne ventrikularne aritmije.[84] Predloženo je i da se razmisli o ugradnji ICD-a čak i nakon blage kliničke pojavnosti.

Nedavna izvješća sugeriraju da su mutacije titna (TTN) čest uzrok DCM-a.[85] Mutacije TTN-a dugo su vremena smatrane kandidatima za uzrok kardiomiopatije, ali veličina gena i prisutnost mnogih varijanti alela su otežali njihovo proučavanje.[86-89] Da bi se nadvladale neke od tih teškoća, Herman i sur.[85] koristili su sekvenciranje nove generacije da bi analizirali gensku sekvencu TTN tražeći mutacije koje mijenjaju cDNA cijelom duljinom (mutacije skraćivanja) kod 792 osobe (321 DCM, 231 HCM i 249 kontrola). TTN mutacije češće su pronađene kod DCM (27%) nego kod HCM (1%) ili kontrole (3%). TTN mutacije se zajednički segregiraju sa DCM u obiteljima s prodornošću bolesti, ali su također uočene i kod 18% naizgled sporadičnih slučajeva. Sekvenciranje TTN bi stoga moglo imati važnu ulogu u genetičkoj evaluaciji DCM pacijenata da bi se pospješila fenotipska dijagnoza, ali visoka frekventnost u kontrolnoj skupini te sporadični slučajevi ukazuju na to da je kod većine TTN mutacija čimbenik podložnosti, a ne uzročni čimbenik.

Važnost epigenetičkih faktora (procesa koji mijenjaju gensku aktivaciju bez mijenjanja DNA sekvence) također je od 2011. bila u središtu pozornosti. U istraživanju koje uspoređuje šire genske metilacije kardiološke DNA u pacijenata s idiopatskim DCM-om i kontrolne skupine, Haas et al otkrili su razlike u metilaciji gena koji su upleteni u načine zatajivanja srca. Ti su geni povezani s razlikama u izrazima mRNA, nalaz koji je dodatno osnažen istraživanjima obavljenima na zebricama.[90]

at 5 years was 33% in the high risk group versus 97% in the low risk group.

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy (DCM) is one of the commonest heart muscle diseases in developed countries. It is defined as systolic impairment and LV dilatation in the absence of previous myocardial infarction. Research highlighting the importance of genetics in the aetiology of inherited and apparently acquired forms of DCM has been a prominent feature over the last few years. Standard symptomatic and prognostic heart failure treatments are the mainstay of patient management but more attention has been paid recently to the importance of aetiology in guiding the approach to management.

Genetic subtypes of DCM

A number of studies have examined the natural history of DCM caused by mutations in the lamin A/C gene (LMNA). This is associated with conduction disease, atrial arrhythmias, heart failure and sudden death and should be suspected when DCM is accompanied by elevated serum creatine kinase, conduction disease or frequent arrhythmias. In these patients, evidence suggests an ICD should be considered at a much lower threshold than in other cases of DCM.[81–83] A multicentre cohort of 269 patients with LMNA mutation identified non-sustained VT, LVEF <45%, male gender and non-missense mutations as risk factors for malignant ventricular arrhythmias.[84] Some authorities suggest ICD implantation should be considered following even mild cardiac expression.

A recent report suggests that titin (TTN) mutations are a common cause of DCM.[85] TTN mutations have long been considered candidate causes of cardiomyopathy, but the size of the gene and the presence of many allelic variants have made it difficult to study.[86–89] To overcome some of these difficulties, Herman and colleagues[85] used next generation sequencing to analyse genomic TTN sequence for mutations that altered fulllength cDNA (truncating mutations) in 792 subjects (312 DCM, 231 HCM and 249 controls). Truncating TTN mutations were found more frequently in DCM (27%) than in HCM (1%) or controls (3%). TTN mutations cosegregated with DCM in families with penetrant disease, but were also found in 18% of apparently sporadic cases. TTN sequencing is therefore likely to have a prominent role in the genetic evaluation of DCM patients in order to facilitate prephenotypic diagnosis, but the high frequency in controls and sporadic cases suggests that the majority of TTN mutants may yet prove to be susceptibility rather than causative factors.

The importance of epigenetic factors (ie, processes that alter gene activation without changing DNA sequence) has also been highlighted since 2011. In a study comparing genome-wide cardiac DNA methylation in patients with idiopathic DCM and controls, Haas *et al* detected differences in the methylation of genes implicated in heart failure pathways. These were associated with differences in mRNA expression, a finding further strengthened by studies in zebra fish.[90] Epigenetics research is particularly advanced in cancer biology, contributing to potential therapeutic/diagnostic biomarker

Epigenetičko istraživanje doživjelo je velik napredak na području biologije raka te pridonosi potencijalnim terapijskim/dijagnostičkim markerima i terapijskim ciljevima,[91-93] no u kardiovaskularnoj genetici još nije došlo do izražaja.

Genske predispozicije upalnim oštećenjima miokarda postaju važna tema.[94] Coxsackie virus, čest uzrok miokarditisa, uzrokuje proteliozu distropina u inficiranim kardiomiocitima.[95-97] Genska oštećenja distrofin-glikoprotein kompleksa, povezana s mišićnom distrofijom, učestalo uzrokuju DCM u slučajevima gdje je CMR često nemoguće razlikovati od miokarditisa.[98] Jedna studija povezuje prisutnost varijanti u receptorima nalik na Toll (*Toll-like receptors*) koji igraju važnu ulogu u urođenim imunološkim reakcijama s lošijom kardiološkom funkcijom kod 158 pacijenata.[99] Naposlijetku, Meder *i sur.*[100] iznose podatke o povezanosti lokusa koji sadrži najvažnije gene histokompatibilnosti (MHC I i II) sa DCM. Autori navode više pojedinačnih polimorfizama nukleotida na kromosomu 6p21. Specifičan je lokus identificiran te je pronađena veza točno lociranih gena koji kodiraju receptore za klasu I i klasu II dugog lanca glavnog sustava tkivne podudarnosti.

Predviđanje ishoda dilatacijske kardiomiopatije

Kao i kod drugih kardiomiopatija, uloga CMR-a u predviđanju rezultata aktivno je područje istraživanja u DCM-u. Nedavni dokazi ukazuju na to da prisutnost srednjostjenčanog LGE otkriva DCM skupinu s povišenim rizikom smrtnosti. Tijekom praćenja nakon zahvata srednje dužine od nešto iznad 5 godina, 27% od 142 DCM pacijenata s LGE je umrlo, u usporedbi s 11% od 330 DCM pacijenata bez LGE.[101] Patofiziološka je osnova ove razlike nejasna.

Podaci koji opisuju dijagnostičku i prognostičku korist CMR surogata za ostale abnormalnosti tkiva, poput edema, difuzne fibroze ili zbrkanih miocita, mogu se očekivati u bliskoj budućnosti.

Neki od najvažnijih podataka iz 2011. sakupljeni su za djecu sa DCM-om. U pedijatrijskom registru s uključenih 1803 pacijenata navedena je stopa pojavnosti od 29% tijekom 5 godina za presađivanje srca, 12,1% bez SCD-a i 2,4% sa SCD-om. Model stratifikacije rizika za SCD zasnovan na podatcima ehokardiografije imao je osjetljivost od 86% i specifičnost od 57%. Značajni faktori su bili dilatacija LV, dob prilikom dijagnoze te stanjivanje stražnje stijenke.[102]

Druga studija, koja je istraživala 175 pedijatrijskih pacijenata s DCM-om utvrdila je učestalost smrti ili transplantacije od 26% u razdoblju od godine dana nakon dijagnoze sa stopom preživljavanja bez smrti ili transplantacije od 56% tijekom 20 godina nakon dijagnoze. Povećan rizik smrti ili transplantacije povezan je s dobi u trenutku dijagnoze, prisustvom obiteljskje kardiomiopatije i niskim početnim vrijednostima frakcije skraćenja LV.[103]

Novosti u liječenju

Terapija matičnim stanicama bila je važna tema tijekom posljednjih godina. Kontrolirana studija petogodišnjeg nasumičnog praćenja 110 pacijenata s DCM-om pokazuje poboljšanje LV funkcije, poboljšanje tolerancije tijekom vježbanja te veću stopu dugoročnog preživljavanja kod pacijenata koji su

and therapeutic targets.[91–93] Its potential in cardiovascular genetics is yet to be realised.

Genetic predisposition to inflammatory myocardial damage is also emerging as an important theme.[94] The Coxsackie virus, a common cause of myocarditis, causes proteolysis of dystrophin in infected cardiomyocytes.[95–97] Genetic defects of the dystrophin– glycoprotein complex, associated with muscular dystrophy, frequently cause a DCM where CMR findings are often indistinguishable from myocarditis.[98] In another study, the presence of variants in Toll-like receptors which play a key role in the innate immune response were associated with poorer cardiac function in 158 patients.[99] Finally, Meder *et al*[100] present data associating the locus containing major histocompatibility genes (MHC I and II) with DCM. The authors identified multiple single nucleotide polymorphisms on chromosome 6p21. A specific locus was identified and an association was found with closely located genes encoding class I and class II major histocompatibility complex heavy chain receptors.

Prediction of outcomes in DCM

As in other cardiomyopathies, the role of CMR in predicting outcomes is an active area of study in DCM. Recent evidence suggests that the presence of midwall LGE identifies a DCM cohort at increased mortality risk. During a median follow-up period of just over 5 years, 27% of 142 DCM with LGE patients died compared with 11% of 330 DCM patients without LGE.[101] The pathophysiological basis of this difference is unclear.

Data describing the diagnostic and prognostic utility of CMR surrogate for other tissue abnormalities, such as oedema, diffuse fibrosis or myocyte disarray, are expected in the near future.

Some of the most important data since 2011 have been in children with DCM. In a paediatric registry population of 1803 patients, a 5-year incidence rate of 29% for heart transplantation, 12.1% non-SCD and 2.4% for SCD are quoted. A risk stratification model for SCD based on echocardiography data had a sensitivity of 86% and 57% specificity. Significant factors were LV dilatation, age at diagnosis and posterior wall thinning.[102]

Another study investigating 175 paediatric patients with DCM reports death or transplantation in 26% within 1 year of diagnosis with a survival free of death or transplant of 56% 20 years after diagnosis. An increased risk for death or transplant was associated with the age at diagnosis, presence of familial cardiomyopathy and lower baseline LV fractional shortening.[103]

Advances in treatment

Stem cell therapy has been a major topic over the course of the last few years. A 5-year follow-up randomised controlled study of 110 patients with DCM shows improved LV function, improved exercise tolerance and greater long term survival in patients who underwent intracoronary stem cell transplantation. Total mortality was 14% in the stem cell group versus 35% in the controls with rates of pump failure of 5% versus 18%. There was no difference in rates of sudden death.[104] A systematic review on 29 preclinical and 15 clinical studies scruti-

podvrgnuti intrakoronarnom presađivanju matičnih stanica. Sveukupna stopa smrtnosti bila je 14% u grupi s matičnim stanicama u usporedbi s 35% u kontrolnoj sa stopom zatajivanja srca od 5% i 18%. Nije bilo razlike u stopi iznenadne smrti.[104] Pregledni članak s uključenih 29 pretkliničkih i 15 kliničkih istraživanja pažljivo je analizirao terapiju matičnim stanicama kao metodu liječenja DCM-a. Većina istraživanja pokazala je blago poboljšanje LVEF u razdoblju nakon terapije matičnim stanicama. Zbog velike heterogenosti u kriterijima uključenja u istraživanje, procedura i mjerenja rezultata, naglašena je potreba za nasumičnim kontroliranim testiranjima.[105]

Istražen je i utjecaj vježbanja kod pacijenata s DCM-om nakon osmotjednog perioda kratkog vježbanja. Zamijećeno je znatno poboljšanje kardiološke funkcije pri odmoru i nakon vježbanja, s najvećim poboljšanjem primijećenim kod neaktivnih pacijenata.[106]

Važnost aktivacije imuniteta još je jedan ključni čimbenik liječenja DCM-a. Male doze atrovastatina smanjile su razine upalnih citokina (IL.6, TNF α), mokraćne kiseline i NT-proBNP-a u malim skupinama pacijenata sa DCM-om.[107]

Sveukupni dokazi ukazuju na poboljšanje stope preživljavanja kod pacijenata s idiopatskim DCM-om. Istraživanje na 603 pacijenta tijekom 3 desetljeća pruža dokaze o utjecaju kliničkih smjernica na pobol i smrtnost. Pacijenti su podijeljeni u 4 podskupine prema razdoblju upisa; zabilježeno je smanjenje stope rizika od 42% po intervalu upisa s obzirom na smrtnost povezanu sa zatajivanjem srca i nagle smrti.[108]

ZAKLJUČAK

Kardiomiopatije su i dalje područje intenzivnog istraživanja u literaturi. Dok je spektar oboljenja značajan i nastavlja se širiti, teme su jako slične među kardiomiopatskim podtipovima, s velikim naglaskom na točnoj dijagnozi, stratifikaciji bolesti i liječenju ovisno o etiologiji. Napredci u ovim područjima će ovisiti o znanosti otkrivanja i primjeni omične tehnologije, ali najveći će uvidi najvjerojatnije biti posljedica velikih multicentričnih suradnji. Svi dokazi ukazuju na to da će nadolazeće godine donijeti sa sobom značajne napretke.

nised stem cell therapy as a treatment for DCM. The majority of studies showed a modest improvement of LVEF after cell therapy during follow-up. Due to the large heterogeneity in criteria for inclusion, procedure and outcome measure, the need for randomised controlled trials was stressed.[105]

Effect of exercise has been evaluated in patients with DCM following an 8-week period of short term exercise. Significant improvement in cardiac function at rest and following exercise was reported with sedentary patients having the greatest improvement.[106]

The importance of immune activation is another focus for therapy in DCM. Atorvastatin in a small dose reduced the levels of inflammatory cytokines (IL-6, TNF α), uric acid and N-terminal pro-brain natriuretic peptide in a small cohort of patients with DCM.[107]

Overall evidence suggests improving survival in patients with idiopathic DCM. A study of 603 patients over three decades gives evidence for the impact of clinical guidelines on morbidity and mortality. Patients were subdivided in four enrolment periods and a 42% risk reduction per enrolment interval with regard to heart failure-related mortality and sudden death was reported.[108]

SUMMARY

Cardiomyopathies continue to be an area of intense interest in the literature. While the spectrum of disease is considerable and continues to expand, the themes are very similar between cardiomyopathy subtypes, with great emphasis on accurate diagnosis, disease stratification and aetiology driven therapy. Advances in these areas will depend on discovery science and the application of omic technologies, but the greatest insights are likely to emerge from large scale multicentre collaborations. All the evidence suggests that the next few years will be one of considerable advance.

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LITERATURE

1. Guttmann OP, Rahman MS, O'Mahony C, et al. Atrial fibrillation and thromboembolism in patients with hypertrophic cardiomyopathy: systematic review. Heart. 2014;100:6 465–72.
2. Maron BJ, Gardin JM, Flack JM, et al. Prevalence of hypertrophic cardiomyopathy in a general population of young adults: echocardiographic analysis of 4111 subjects in the CARDIA study. Circulation. 1995;92:785–9. **DOI:** http://dx.doi.org/10.1161/01.CIR.92.4.785
3. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. Lancet. 2004;363:1881–91. **DOI:** http://dx.doi.org/10.1016/S0140-6736(04)16358-7
4. Sado DM, Flett AS, Banypersad SM, et al. Cardiovascular magnetic resonance measurement of myocardial extracellular volume in health and disease. Heart. 2012;98:1436–41. **DOI:** http://dx.doi.org/10.1136/heartjnl-2012-302346
5. Puntmann VO, Voigt T, Chen Z, et al. Native T1 mapping in differentiation of normal myocardium from diffuse disease in hypertrophic and dilated cardiomyopathy. JACC Cardiovasc Imaging. 2013;6:475–84. **DOI:** http://dx.doi.org/10.1016/j.jcmg.2012.08.019
6. Sado DM, White SK, Piechnik SK, et al. Identification and assessment of Anderson-Fabry disease by cardiovascular magnetic resonance noncontrast myocardial T1 mapping. Circ Cardiovasc Imaging. 2013;6:392–8. **DOI:** http://dx.doi.org/10.1161/CIRCIMAGING.112.000070
7. Ferreira VM, Piechnik SK, Dall'armellina E, et al. Non-contrast T1-mapping detects acute myocardial edema with high diagnostic accuracy: a comparison to T2-weighted cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2012;14:42. **DOI:** http://dx.doi.org/10.1186/1532-429X-14-42

8. Valente AM, Lakdawala NK, Powell AJ, et al. Comparison of echocardiographic and cardiac magnetic resonance imaging in hypertrophic cardiomyopathy sarcomere mutation carriers without left ventricular hypertrophy. Circ Cardiovasc Genet. 2013;6:230–7. **DOI:** http://dx.doi.org/10.1161/CIRCGENETICS.113.000037
9. Ho CY, Abbasi SA, Neilan TG, et al. T1 measurements identify extracellular volume expansion in hypertrophic cardiomyopathy sarcomere mutation carriers with and without left ventricular hypertrophy. Circ Cardiovasc Imaging. 2013;6:415–22. **DOI:** http://dx.doi.org/10.1161/CIRCIMAGING.112.000333
10. Greulich S, Schumm J, Grun S, et al. Incremental value of late gadolinium enhancement for management of patients with hypertrophic cardiomyopathy. Am J Cardiol. 2012;110:1207–12. **DOI:** http://dx.doi.org/10.1016/j.amjcard.2012.05.064
11. Green JJ, Berger JS, Kramer CM, et al. Prognostic value of late gadolinium enhancement in clinical outcomes for hypertrophic cardiomyopathy. JACC Cardiovasc Imaging. 2012;5:370–7. **DOI:** http://dx.doi.org/10.1016/j.jcmg.2011.11.021
12. van Veldhuisen DJ, Linssen GC, Jaarsma T, et al. B-type natriuretic peptide and prognosis in heart failure patients with preserved and reduced ejection fraction. J Am Coll Cardiol. 2013;61:1498–506. **DOI:** http://dx.doi.org/10.1016/j.jacc.2012.12.044
13. Geske JB, McKie PM, Ommen SR, et al. B-type natriuretic Peptide and survival in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;61:2456–60. **DOI:** http://dx.doi.org/10.1016/j.jacc.2013.04.004
14. D'Amato R, Tomberli B, Castelli G, et al. Prognostic value of N-terminal pro-brain natriuretic peptide in outpatients with hypertrophic cardiomyopathy. Am J Cardiol. 2013;112:1190–6. **DOI:** http://dx.doi.org/10.1016/j.amjcard.2013.06.018
15. Coats CJ, Gallagher MJ, Foley M, et al. Relation between serum N-terminal pro-brain natriuretic peptide and prognosis in patients with hypertrophic cardiomyopathy. Eur Heart J. 2013;34:2529–37. **DOI:** http://dx.doi.org/10.1093/eurheartj/eht070
16. Kubo T, Kitaoka H, Yamanaka S, et al. Significance of high-sensitivity cardiac troponin T in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;62:1252–9. **DOI:** http://dx.doi.org/10.1016/j.jacc.2013.03.055
17. Nistri S, Olivotto I, Maron MS, et al. beta Blockers for prevention of exercise-induced left ventricular outf low tract obstruction in patients with hypertrophic cardiomyopathy. Am J Cardiol. 2012;110:715–9. **DOI:** http://dx.doi.org/10.1016/j.amjcard.2012.04.051
18. Sherrid MV, Shetty A, Winson G, et al. Treatment of obstructive hypertrophic cardiomyopathy symptoms and gradient resistant to first-line therapy with beta-blockade or verapamil. Circ Heart Fail. 2013;6:694–702. **DOI:** http://dx.doi.org/10.1161/CIRCHEARTFAILURE.112.000122
19. Sorajja P, Ommen SR, Holmes DR Jr, et al. Survival after alcohol septal ablation for obstructive hypertrophic cardiomyopathy. Circulation. 2012;126:2374–80. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.111.076257
20. Jensen MK, Prinz C, Horstkotte D, et al. Alcohol septal ablation in patients with hypertrophic obstructive cardiomyopathy: low incidence of sudden cardiac death and reduced risk profile. Heart. 2013;99:1012–7. **DOI:** http://dx.doi.org/10.1136/heartjnl-2012-303339
21. Orme NM, Sorajja P, Dearani JA, et al. Comparison of surgical septal myectomy to medical therapy alone in patients with hypertrophic cardiomyopathy and syncope. Am J Cardiol. 2013;111:388–92. **DOI:** http://dx.doi.org/10.1016/j.amjcard.2012.10.014
22. Iacovoni A, Spirito P, Simon C, et al. A contemporary European experience with surgical septal myectomy in hypertrophic cardiomyopathy. Eur Heart J. 2012;33:2080–7. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehs064
23. Desai MY, Bhonsale A, Smedira NG, et al. Predictors of long-term outcomes in symptomatic hypertrophic obstructive cardiomyopathy patients undergoing surgical relief of left ventricular outf low tract obstruction. Circulation. 2013;128:209–16. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.112.000849
24. Galve E, Sambola A, Saldana G, et al. Late benefits of dual-chamber pacing in obstructive hypertrophic cardiomyopathy: a 10-year follow-up study. Heart. 2010;96:352–6. **DOI:** http://dx.doi.org/10.1136/hrt.2008.158915
25. Mohiddin SA, Page SP. Long-term benefits of pacing in obstructive hypertrophic cardiomyopathy. Heart. 2010;96:328–30. **DOI:** http://dx.doi.org/10.1136/hrt.2009.173765
26. Kappenberger LJ, Linde C, Jeanrenaud X, et al. Clinical progress after randomized on/off pacemaker treatment for hypertrophic obstructive cardiomyopathy. Pacing in Cardiomyopathy (PIC) Study Group. Europace. 1999;1:77–84. **DOI:** http://dx.doi.org/10.1053/eupc.1998.0024
27. Maron BJ, Nishimura RA, McKenna WJ, et al. Assessment of permanent dual-chamber pacing as a treatment for drug-refractory symptomatic patients with obstructive hypertrophic cardiomyopathy. A randomized, double-blind, crossover study (M-PATHY). Circulation. 1999;99:2927–33. **DOI:** http://dx.doi.org/10.1161/01.CIR.99.22.2927
28. Qintar M, Morad A, Alhawasli H, et al. Pacing for drug-refractory or drug-intolerant hypertrophic cardiomyopathy. Cochrane Database Syst Rev. 2012; (5):CD008523. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/22592731?dopt=Abstract
29. Schinkel AF, Vriesendorp PA, Sijbrands EJ, et al. Outcome and complications after implantable cardioverter defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. Circ Heart Fail. 2012;5:552–9. **DOI:** http://dx.doi.org/10.1161/CIRCHEARTFAILURE.112.969626
30. O'Mahony C, Lambiase PD, Quarta G, et al. The long-term survival and the risks and benefits of implantable cardioverter defibrillators in patients with hypertrophic cardiomyopathy. Heart. 2012;98:116–25. **DOI:** http://dx.doi.org/10.1136/hrt.2010.217182
31. Bos JM, Maron BJ, Ackerman MJ, et al. Role of family history of sudden death in risk stratification and prevention of sudden death with implantable defibrillators in hypertrophic cardiomyopathy. Am J Cardiol. 2010;106:1481–6. **DOI:** http://dx.doi.org/10.1016/j.amjcard.2010.06.077
32. Christiaans I, van Engelen K, van Langen IM, et al. Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers. Europace. 2010;12:313–21. **DOI:** http://dx.doi.org/10.1093/europace/eup431
33. O'Mahony C, Tome-Esteban M, Lambiase PD, et al. A validation study of the 2003 American College of Cardiology/European Society of Cardiology and 2011 American College of Cardiology Foundation/American Heart Association risk stratification and treatment algorithms for sudden cardiac death in patients with hypertrophic cardiomyopathy. Heart. 2013;99:534–41. **DOI:** http://dx.doi.org/10.1136/heartjnl-2012-303271
34. Elliott PM, Gimeno JR, Tome MT, et al. Left ventricular outf low tract obstruction and sudden death risk in patients with hypertrophic cardiomyopathy. Eur Heart J. 2006;27:1933–41. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehl041
35. Maron BJ, Rowin EJ, Casey SA, et al. Risk stratification and outcome of patients with hypertrophic cardiomyopathy >=60 years of age. Circulation. 2013;127:585–93. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.112.136085
36. Moak JP, Leifer ES, Tripodi D, et al. Long-term follow-up of children and adolescents diagnosed with hypertrophic cardiomyopathy: risk factors for adverse arrhythmic events. Pediatr Cardiol. 2011;32:1096–105. **DOI:** http://dx.doi.org/10.1007/s00246-011-9967-y
37. Maron BJ, Spirito P, Ackerman MJ, et al. Prevention of sudden cardiac death with implantable cardioverter-defibrillators in children and adolescents with hypertrophic cardiomyopathy. J Am Coll Cardiol. 2013;61:1527–35. **DOI:** http://dx.doi.org/10.1016/j.jacc.2013.01.037
38. Ingles J, McGaughran J, Scuffham PA, et al. A cost-effectiveness model of genetic testing for the evaluation of families with hypertrophic cardiomyopathy. Heart. 2012;98:625–30. **DOI:** http://dx.doi.org/10.1136/heartjnl-2011-300368
39. Wordsworth S, Leal J, Blair E, et al. DNA testing for hypertrophic cardiomyopathy: a cost-effectiveness model. Eur Heart J. 2010;31:926–35. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehq067
40. Jensen MK, Havndrup O, Christiansen M, et al. Penetrance of hypertrophic cardiomyopathy in children and adolescents: a 12-year follow-up study of clinical screening and predictive genetic testing. Circulation. 2013;127:48–54. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/23197161?dopt=Abstract
41. Lopes LR, Rahman MS, Elliott PM. A systematic review and meta-analysis of genotype-phenotype associations in patients with hypertrophic cardiomyopathy caused by sarcomeric protein mutations. Heart. 2013;99:1800–11. **DOI:** http://dx.doi.org/10.1136/heartjnl-2013-303939
42. Liang P, Lan F, Lee AS, et al. Drug screening using a library of human induced pluripotent stem cell-derived cardiomyocytes reveals disease-specific patterns of cardiotoxicity. Circulation. 2013;127:1677–91. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.113.001883
43. Lan F, Lee AS, Liang P, et al. Abnormal calcium handling properties underlie familial hypertrophic cardiomyopathy pathology in patient-specific induced pluripotent stem cells. Cell Stem Cell. 2013;12:101–13. **DOI:** http://dx.doi.org/10.1016/j.stem.2012.10.010

44. Corrado D, Basso C, Pilichou K, et al. Molecular biology and clinical management of arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart. 2011;97:530–9. **DOI:** http://dx.doi.org/10.1136/hrt.2010.193276
45. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J. 2010;31:806–14. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehq025
46. Protonotarios N, Anastasakis A, Antoniades L, et al. Arrhythmogenic right ventricular cardiomyopathy/dysplasia on the basis of the revised diagnostic criteria in affected families with desmosomal mutations. Eur Heart J. 2011;32:1097–104. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehr043
47. Quarta G, Muir A, Pantazis A, et al. Familial evaluation in arrhythmogenic right ventricular cardiomyopathy: impact of genetics and revised task force criteria. Circulation. 2011;123:2701–9. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.110.976936
48. Basso C, Corrado D, Thiene G. Arrhythmogenic right ventricular cardiomyopathy in athletes: diagnosis, management, and recommendations for sport activity. Cardiol Clin. 2007;25:415–22. [vi.] **DOI:** http://dx.doi.org/10.1016/j.ccl.2007.08.009
49. Zaidi A, Ghani S, Sheikh N, et al. Clinical significance of electrocardiographic right ventricular hypertrophy in athletes: comparison with arrhythmogenic right ventricular cardiomyopathy and pulmonary hypertension. Eur Heart J. 2013;34:3649–56. **DOI:** http://dx.doi.org/10.1093/eurheartj/eht391
50. Munkholm J, Christensen AH, Svendsen JH, et al. Usefulness of immunostaining for plakoglobin as a diagnostic marker of arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol. 2012;109:272–5. **DOI:** http://dx.doi.org/10.1016/j.amjcard.2011.08.044
51. Asimaki A, Tandri H, Duffy ER, et al. Altered desmosomal proteins in granulomatous myocarditis and potential pathogenic links to arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythm Electrophysiol. 2011;4:743–52. **DOI:** http://dx.doi.org/10.1161/CIRCEP.111.964890
52. Gomes J, Finlay M, Ahmed AK, et al. Electrophysiological abnormalities precede overt structural changes in arrhythmogenic right ventricular cardiomyopathy due to mutations in desmoplakin-A combined murine and human study. Eur Heart J. 2012;33:1942–53. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehr472
53. Cox MG, van der Zwaag PA, van der Werf C, et al. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: pathogenic desmosome mutations in index-patients predict outcome of family screening: Dutch arrhythmogenic right ventricular dysplasia/cardiomyopathy genotype-phenotype follow-up study. Circulation. 2011;123:2690–700. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.110.988287
54. Li Mura IE, Bauce B, Nava A, et al. Identification of a PKP2 gene deletion in a family with arrhythmogenic right ventricular cardiomyopathy. Eur J Hum Genet. 2013;21:1226–31. **DOI:** http://dx.doi.org/10.1038/ejhg.2013.39
55. van der Zwaag PA, van Rijsingen IA, de Ruiter R, et al. Recurrent and founder mutations in the Netherlands-Phospholamban p.Arg14del mutation causes arrhythmogenic cardiomyopathy. Neth Heart J. 2013;21:286–93. **DOI:** http://dx.doi.org/10.1007/s12471-013-0401-3
56. Baskin B, Skinner JR, Sanatani S, et al. TMEM43 mutations associated with arrhythmogenic right ventricular cardiomyopathy in non-Newfoundland populations. Hum Genet. 2013;132:1245–52. **DOI:** http://dx.doi.org/10.1007/s00439-013-1323-2
57. van Hengel J, Calore M, Bauce B, et al. Mutations in the area composita protein alphaT-catenin are associated with arrhythmogenic right ventricular cardiomyopathy. Eur Heart J. 2013;34:201–10. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehs373
58. Gerull B, Kirchner F, Chong J, et al. A homozygous founder mutation in desmocollin-2 (DSC2) causes arrhythmogenic cardiomyopathy in the Hutterite population. Circ Cardiovasc Genet. 2013;6:327–36. **DOI:** http://dx.doi.org/10.1161/CIRCGENETICS.113.000097
59. Haywood AF, Merner ND, Hodgkinson KA, et al. Recurrent missense mutations in TMEM43 (ARVD5) due to founder effects cause arrhythmogenic cardiomyopathies in the UK and Canada. Eur Heart J. 2013;34:1002–11. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehs383
60. Groeneweg JA, van der Zwaag PA, Jongbloed JD, et al. Left-dominant arrhythmogenic cardiomyopathy in a large family: associated desmosomal or nondesmosomal genotype? Heart Rhythm. 2013;10:548–59. **DOI:** http://dx.doi.org/10.1016/j.hrthm.2012.12.020
61. Quarta G, Syrris P, Ashworth M, et al. Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. Eur Heart J. 2012;33:1128–36. **DOI:** http://dx.doi.org/10.1093/eurheartj/ehr451
62. Marcus FI, Edson S, Towbin JA. Genetics of arrhythmogenic right ventricular cardiomyopathy: a practical guide for physicians. J Am Coll Cardiol. 2013;61:1945–8. **DOI:** http://dx.doi.org/10.1016/j.jacc.2013.01.073
63. Kapplinger JD, Landstrom AP, Salisbury BA, et al. Distinguishing arrhythmogenic right ventricular cardiomyopathy/dysplasia-associated mutations from background genetic noise. J Am Coll Cardiol. 2011;57:2317–27. **DOI:** http://dx.doi.org/10.1016/j.jacc.2010.12.036
64. Kim C, Wong J, Wen J, et al. Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs. Nature. 2013;494:105–10. **DOI:** http://dx.doi.org/10.1038/nature11799
65. Corrado D, Basso C, Rizzoli G, et al. Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol. 2003;42:1959–63. **DOI:** http://dx.doi.org/10.1016/j.jacc.2003.03.002
66. Fabritz L, Fortmuller L, Yu TY, et al. Can preload-reducing therapy prevent disease progression in arrhythmogenic right ventricular cardiomyopathy? Experimental evidence and concept for a clinical trial. Prog Biophys Mol Biol. 2012;110:340–6. **DOI:** http://dx.doi.org/10.1016/j.pbiomolbio.2012.08.010
67. Maron BJ, Chaitman BR, Ackerman MJ, et al. Recommendations for physical activity and recreational sports participation for young patients with genetic cardiovascular diseases. Circulation. 2004;109:2807–16. **DOI:** http://dx.doi.org/10.1161/01.CIR.0000128363.85581.E1
68. Maron BJ, Ackerman MJ, Nishimura RA, et al. Task Force 4: HCM and other cardiomyopathies, mitral valve prolapse, myocarditis, and Marfan syndrome. J Am Coll Cardiol. 2005;45:1340–5. **DOI:** http://dx.doi.org/10.1016/j.jacc.2005.02.011
69. James CA, Bhonsale A, Tichnell C, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy associated desmosomal mutation carriers. J Am Coll Cardiol. 2013;62:1290–7. **DOI:** http://dx.doi.org/10.1016/j.jacc.2013.06.033
70. Fabritz L, Hoogendijk MG, Scicluna BP, et al. Load-reducing therapy prevents development of arrhythmogenic right ventricular cardiomyopathy in plakoglobin-deficient mice. J Am Coll Cardiol. 2011;57:740–50. **DOI:** http://dx.doi.org/10.1016/j.jacc.2010.09.046
71. Dalal D, Jain R, Tandri H, et al. Long-term efficacy of catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia/ cardiomyopathy. J Am Coll Cardiol. 2007;50:432–40. **DOI:** http://dx.doi.org/10.1016/j.jacc.2007.03.049
72. Verma A, Kilicaslan F, Schweikert RA, et al. Short- and long-term success of substrate-based mapping and ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia. Circulation. 2005;111:3209–16. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.104.510503
73. Philips B, Madhavan S, James C, et al. Outcomes of catheter ablation of ventricular tachycardia in arrhythmogenic right ventricular dysplasia/ cardiomyopathy. Circ Arrhythm Electrophysiol. 2012;5:499–505. **DOI:** http://dx.doi.org/10.1161/CIRCEP.111.968677
74. Basso C, Corrado D, Bauce B, et al. Arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythm Electrophysiol. 2012;5:1233–46. **DOI:** http://dx.doi.org/10.1161/CIRCEP.111.962035
75. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol. 2006;48:e247–346. **PubMed:** http://www.ncbi.nlm.nih.gov/pubmed/16949478?dopt=Abstract
76. Schinkel AF. Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and inappropriate interventions, and complications. Circ Arrhythm Electrophysiol. 2013;6:562–8. **DOI:** http://dx.doi.org/10.1161/CIRCEP.113.000392
77. te Riele AS, Bhonsale A, James CA, et al. Incremental value of cardiac magnetic resonance imaging in arrhythmic risk stratification of arrhythmogenic right ventricular dysplasia/cardiomyopathy associated desmosomal mutation carriers. J Am Coll Cardiol. 2013;62:1761–9. **DOI:** http://dx.doi.org/10.1016/j.jacc.2012.11.087
78. Deac M, Alpendurada F, Fanaie F, et al. Prognostic value of cardiovascular magnetic resonance in patients with suspected arrhythmogenic right ventricular cardiomyopathy. Int J Cardiol. 2013;168:3514–21. **DOI:** http://dx.doi.org/10.1016/j.ijcard.2013.04.208

79. Hong TT, Cogswell R, James CA, et al. Plasma BIN1 correlates with heart failure and predicts arrhythmia in patients with arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm. 2012;9:961–7. **DOI:** http://dx.doi.org/10.1016/j.hrthm.2012.01.024
80. Bhonsale A, James CA, Tichnell C, et al. Risk stratification in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. Circ Arrhythm Electrophysiol. 2013;6:569–78. **DOI:** http://dx.doi.org/10.1161/CIRCEP.113.000233
81. van Berlo JH, de Voogt WG, van der Kooi AJ, et al. Meta-analysis of clinical characteristics of 299 carriers of LMNA gene mutations: do lamin A/C mutations portend a high risk of sudden death? J Mol Med (Berl). 2005;83:79–83. **DOI:** http://dx.doi.org/10.1007/s00109-004-0589-1
82. Meune C, Van Berlo JH, Anselme F, et al. Primary prevention of sudden death in patients with lamin A/C gene mutations. N Engl J Med. 2006;354:209–10. **DOI:** http://dx.doi.org/10.1056/NEJMc052632
83. Taylor MR, Fain PR, Sinagra G, et al. Natural history of dilated cardiomyopathy due to lamin A/C gene mutations. J Am Coll Cardiol. 2003;41:771–80. **DOI:** http://dx.doi.org/10.1016/S0735-1097(02)02954-6
84. van Rijsingen IA, Arbustini E, Elliott PM, et al. Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a European cohort study. J Am Coll Cardiol. 2012;59(5):493–500. **DOI:** http://dx.doi.org/10.1016/j.jacc.2011.08.078
85. Herman DS, Lam L, Taylor MR, et al. Truncations of titin causing dilated cardiomyopathy. N Engl J Med. 2012;366:619–28. **DOI:** http://dx.doi.org/10.1056/NEJMoa1110186
86. Gerull B, Gramlich M, Atherton J, et al. Mutations of TTN, encoding the giant muscle filament titin, cause familial dilated cardiomyopathy. Nat Genet. 2002;30:201–4. **DOI:** http://dx.doi.org/10.1038/ng815
87. Gerull B, Atherton J, Geupel A, et al. Identification of a novel frameshift mutation in the giant muscle filament titin in a large Australian family with dilated cardiomyopathy. J Mol Med (Berl). 2006;84:478–83. **DOI:** http://dx.doi.org/10.1007/s00109-006-0060-6
88. Siu BL, Niimura H, Osborne JA, et al. Familial dilated cardiomyopathy locus maps to chromosome 2q31. Circulation. 1999;99:1022–6. **DOI:** http://dx.doi.org/10.1161/01.CIR.99.8.1022
89. Satoh M, Takahashi M, Sakamoto T, et al. Structural analysis of the titin gene in hypertrophic cardiomyopathy: identification of a novel disease gene. Biochem Biophys Res Commun. 1999;262:411–7. **DOI:** http://dx.doi.org/10.1006/bbrc.1999.1221
90. Haas J, Frese KS, Park YJ, et al. Alterations in cardiac DNA methylation in human dilated cardiomyopathy. EMBO Mol Med. 2013;5:413–29. **DOI:** http://dx.doi.org/10.1002/emmm.201201553
91. Coppedè F. Epigenetic biomarkers of colorectal cancer: focus on DNA methylation. Cancer Lett. 2014;342:238–47. **DOI:** http://dx.doi.org/10.1016/j.canlet.2011.12.030
92. Litzow MR. Novel therapeutic approaches for acute lymphoblastic leukemia. Hematol Oncol Clin North Am. 2011;25:1303–17. **DOI:** http://dx.doi.org/10.1016/j.hoc.2011.09.019
93. Herceg Z, Vaissiere T. Epigenetic mechanisms and cancer: an interface between the environment and the genome. Epigenetics. 2011;6:804–19. **DOI:** http://dx.doi.org/10.4161/epi.6.7.16262
94. Mavrogeni S, Spargias C, Bratis C, et al. Myocarditis as a precipitating factor for heart failure: evaluation and 1-year follow-up using cardiovascular magnetic resonance and endomyocardial biopsy. Eur J Heart Fail. 2011;13:830–7. **DOI:** http://dx.doi.org/10.1093/eurjhf/hfr052
95. Badorff C, Knowlton KU. Dystrophin disruption in enterovirus-induced myocarditis and dilated cardiomyopathy: from bench to bedside. Med Microbiol Immunol (Berl). 2004;193:121–6. **DOI:** http://dx.doi.org/10.1007/s00430-003-0189-7
96. Badorff C, Fichtlscherer B, Rhoads RE, et al. Nitric oxide inhibits dystrophin proteolysis by coxsackieviral protease 2A through S-nitrosylation: a protective mechanism against enteroviral cardiomyopathy. Circulation. 2000;102:2276–81. **DOI:** http://dx.doi.org/10.1161/01.CIR.102.18.2276
97. Badorff C, Lee GH, Knowlton KU. Enteroviral cardiomyopathy: bad news for the dystrophin-glycoprotein complex. Herz. 2000;25:227–32. **DOI:** http://dx.doi.org/10.1007/s000590050011
98. Mavrogeni S, Papavasiliou A, Spargias K, et al. Myocardial inf lammation in Duchenne Muscular Dystrophy as a precipitating factor for heart failure: a prospective study. BMC Neurol. 2010;10:33. **DOI:** http://dx.doi.org/10.1186/1471-2377-10-33
99. Riad A, Meyer SH, Weitmann K, et al. Variants of Toll-like receptor 4 predict cardiac recovery in patients with dilated cardiomyopathy. J Biol Chem. 2012;287:27236–43. **DOI:** http://dx.doi.org/10.1074/jbc.M112.369728
100. Meder B, Ruhle F, Weis T, et al. A genome-wide association study identifies 6p21 as novel risk locus for dilated cardiomyopathy. Eur Heart J. 2014;35(16):1069-77. **DOI:** http://dx.doi.org/10.1093/eurheartj/eht251
101. Gulati A, Jabbour A, Ismail TF, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA. 2013;309:896–908. **DOI:** http://dx.doi.org/10.1001/jama.2013.1363
102. Pahl E, Sleeper LA, Canter CE, et al. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. J Am Coll Cardiol. 2012;59:607–15. **DOI:** http://dx.doi.org/10.1016/j.jacc.2011.10.878
103. Alexander PM, Daubeney PE, Nugent AW, et al. Long-term outcomes of dilated cardiomyopathy diagnosed during childhood: results from a national population-based study of childhood cardiomyopathy. Circulation. 2013;128:2039–46. **DOI:** http://dx.doi.org/10.1161/CIRCULATIONAHA.113.002767
104. Vrtovec B, Poglajen G, Lezaic L, et al. Effects of intracoronary CD34+ stem cell transplantation in nonischemic dilated cardiomyopathy patients: 5-year follow-up. Circ Res. 2013;112:165–73. **DOI:** http://dx.doi.org/10.1161/CIRCRESAHA.112.276519
105. Gho JM, Kummeling GJ, Koudstaal S, et al. Cell therapy, a novel remedy for dilated cardiomyopathy? A systematic review. J Card Fail. 2013;19:494–502. **DOI:** http://dx.doi.org/10.1016/j.cardfail.2013.05.006
106. Holloway CJ, Dass S, Suttie JJ, et al. Exercise training in dilated cardiomyopathy improves rest and stress cardiac function without changes in cardiac high energy phosphate metabolism. Heart. 2012;98:1083–90. **DOI:** http://dx.doi.org/10.1136/heartjnl-2012-302145
107. Bielecka-Dabrowa A, Mikhailidis DP, Rizzo M, et al. The inf luence of atorvastatin on parameters of inf lammation left ventricular function, hospitalizations and mortality in patients with dilated cardiomyopathy–5-year follow-up. Lipids Health Dis. 2013;12:47. **DOI:** http://dx.doi.org/10.1186/1476-511X-12-47
108. Castelli G, Fornaro A, Ciaccheri M, et al. Improving survival rates of patients with idiopathic dilated cardiomyopathy in tuscany over three decades: impact of evidence-based management. Circ Heart Fail. 2013;6:913–21. **DOI:** http://dx.doi.org/10.1161/CIRCHEARTFAILURE.112.000120