Co nového u dilatační kardiomyopatie?

CO NÁM PŘINESE GENETICKÉ VYŠETŘENÍ?

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XXVII. Výroční sjezd ČKS, 13. květen 2019, Brno

Co nám přinese genetické vyšetření?

- Odhad rizika výskytu DKMP u rodinných příslušníků (genetické poradenství), současná doporučení.

- Odhad prognózy onemocnění
  A) arytmický fenotyp DKMP
  B) vztah k reverzní remodelaci LKS

- Interakce genotypu a zevního prostředí- alkoholická KMP

Důkazy pro genetickou etiologii DKMP - familiární výskyt + molekulárně-genetické vyšetření

- Pro genetické podmínění DKMP svědčí pozitivní rodinná anamnéza onemocnění u cca 20% nemocných.

- Při systematickém vyšetření příbuzných 1. stupně pomocí EKG a echokardiografie je možno prokázat familiární výskyt DKMP až u 30-35% případů.

- Zavedení metod sekvenace nové generace (NGS) zvýšila výtěžnost molekulárně-genetické vyšetření u familiární DKMP z 1/3 až na 2/3 případů.

Molekulárně-genetické příčiny DKMP (více než 40 genů, většinou s AD dědičností)

Table 1 DCM Gene Ontology

Sarcome	Cytoskeleton	Z-disc	Nuclear envelope
ACTC1	*DMD*	*TCAP*	*LMNA*
MYH7	*DES*	*CSRP3*	*TMPO*
MYH6	*LDB3*	*ACTN2*	Gamma secretase activity
MYBPC3	*SGCD*	*MYPN*	*PSEN1*
TNNT2	*PDLIM3*	*ANKRD1*	*PSEN2*
TNNC1	*VCL*	*NEBL*	Transcription factor
TNNI3	*RYAB*	*NEXN*	*EYA4*
TPM1	*ILK*		RNA binding
TTN	*LAMA4*		*RBM20*
Ion channel	Mitochondrial		Co-chaperone, heat shock proteins
ABCC9	*TAZ/G4.5*		*BAG3*
SCN5A	Sarcoplasmic reticulum		
	PLN		

JACC Vol. 60, No. 4, 2012
July 24, 2012:283–9

Nejčastější příčiny:

1. trunkující mutace titinu
-25% famil. případů
-18% sporadických případů

2. mutace laminu A/C:
-6 až 8% fam. případů
-4% sporadický případů

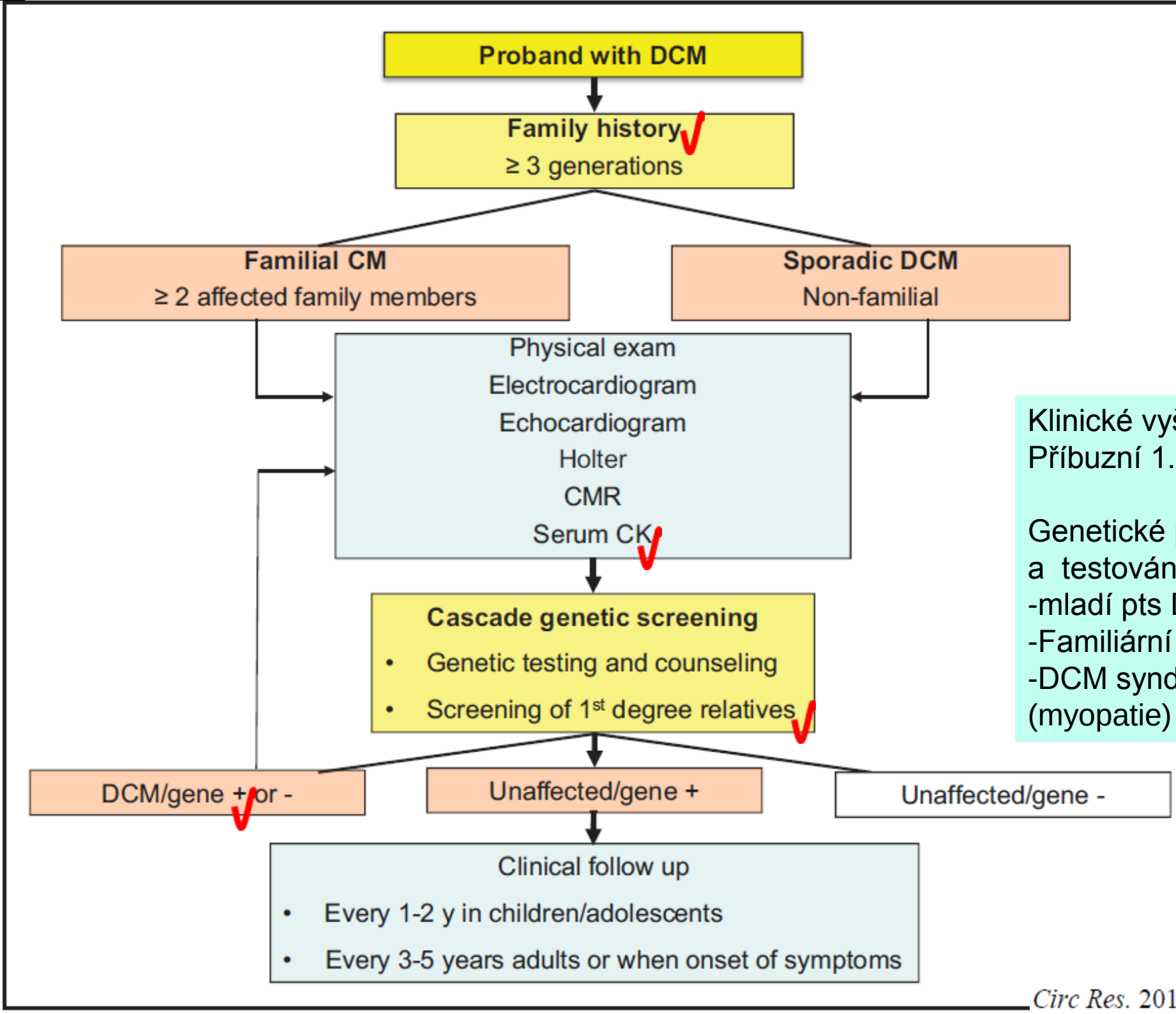
Primární metoda vyšetření NGS (kardiopanel, exomová sekvenace)

- Dříve úspěšná u 30-35% famil. DCM

- Nyní až u 60% případů

1. DOPORUČENÍ KLINICKÉHO A VE VYBRANÝCH PŘÍPADECH I GENETICKÉHO SCREENINGU V RODINÁCH

Racionále: možnost léčby presymptomatické systolické dysfunkce LKS a prevence závažných klinických příhod u příbuzných.



Klinické vyšetření:
Příbuzní 1. stupně

Genetické poradenství a testování:
-mladí pts DCM
-Familiární DCM
-DCM syndromická (myopatie)

Circ Res. 2017;121:731-748

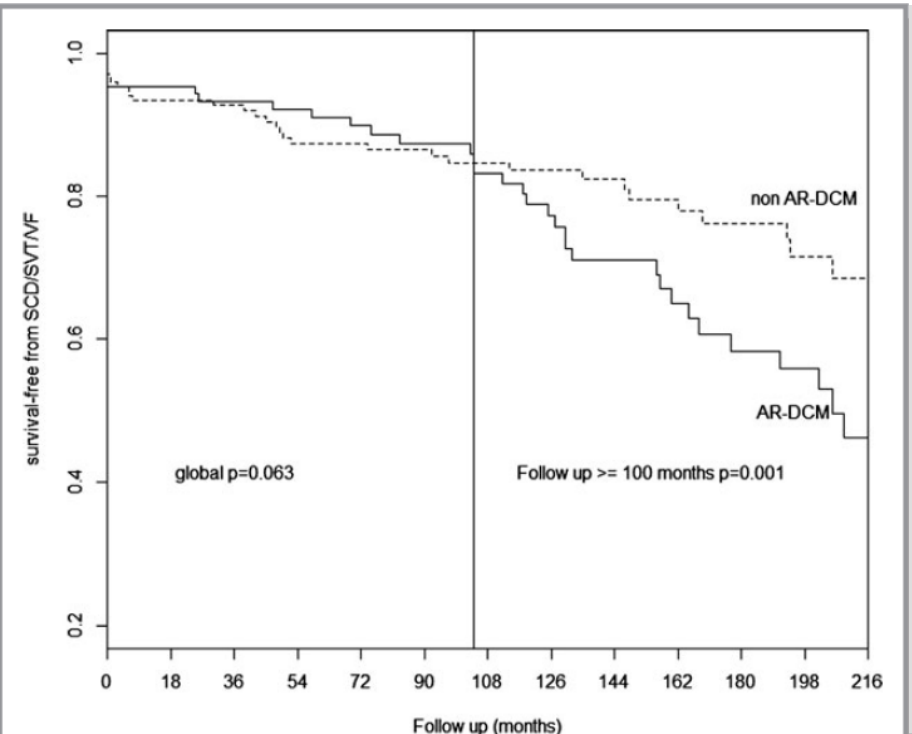
2. PROGNOSTICKÝ VÝZNAM GENETICKÉHO VYŠETŘENÍ- ARYTMICKÝ FENOTYP DKMP

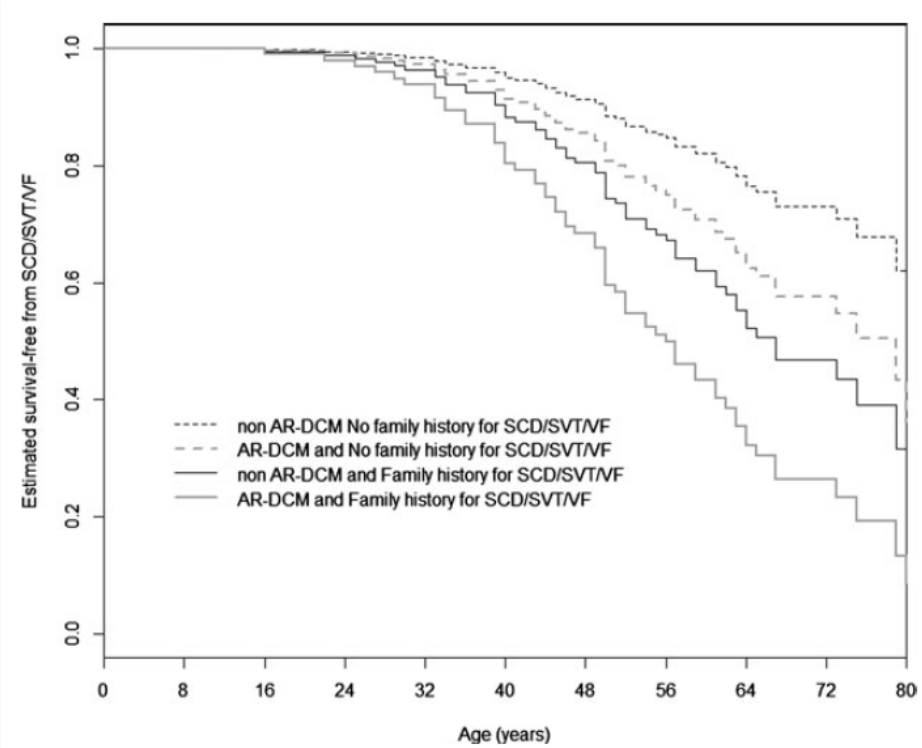
Racionále: přínos primárně preventivní implantace ICD u DKMP oproti ICHS méně přesvědčivý, některé genetické formy DKMP spojeny s vysokým rizikem NSS.

Arrhythmogenic Phenotype in Dilated Cardiomyopathy: Natural History and Predictors of Life-Threatening Arrhythmias

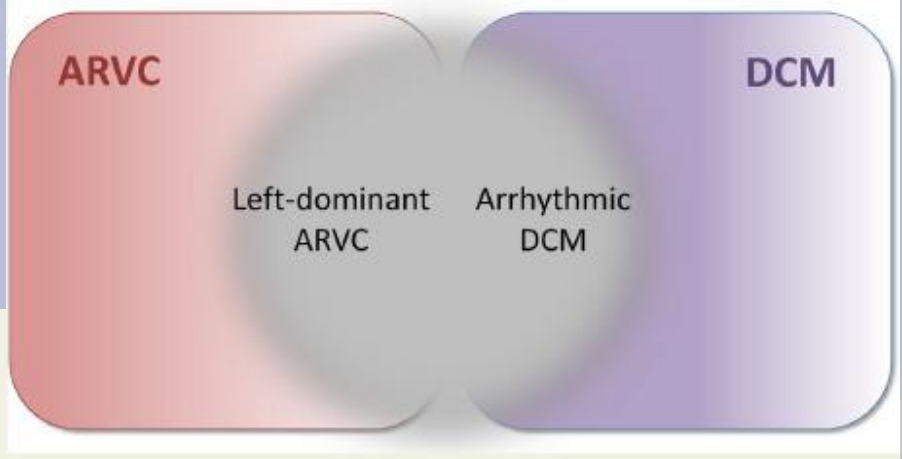
Methods and Results—Two hundred eighty-five patients with a recent diagnosis of DCM (median duration of the disease 1 month, range 0 to 7 months) and who had Holter monitoring at baseline were comprehensively evaluated and followed for 107 months (range 29 to 170 months). AR-DCM was defined by the presence of >1 of the following: unexplained syncope, rapid nonsustained ventricular tachycardia (≥5 beats, >150 bpm), >1000 premature ventricular contractions/24 hours, and >50 ventricular couplets/24 hours, in the absence of overt heart failure. The primary end points were sudden cardiac death (SCD), sustained ventricular tachycardia (SVT), or ventricular fibrillation (VF). The secondary end points were death from congestive heart failure or heart transplantation. Of the 285 patients, 109 (38.2%) met criteria for AR-DCM phenotype. AR-DCM subjects had a higher incidence of SCD/SVT/VF compared with non–AR-DCM patients (30.3% vs 17.6%, *P*=0.022), with no difference in the secondary end points. A family history of SCD/SVT/VF and the AR-DCM phenotype were statistically significant and cumulative predictors of SCD/SVT/VF.

Conclusions—One-third of DCM patients may have an arrhythmogenic phenotype associated with increased risk of arrhythmias during follow-up. A family history of ventricular arrhythmias in DCM predicts a poor prognosis and increased risk of SCD. **(*J Am Heart Assoc*. 2015;4:e002149 doi: 10.1161/JAHA.115.002149)**





Arytmický fenotyp DKMP



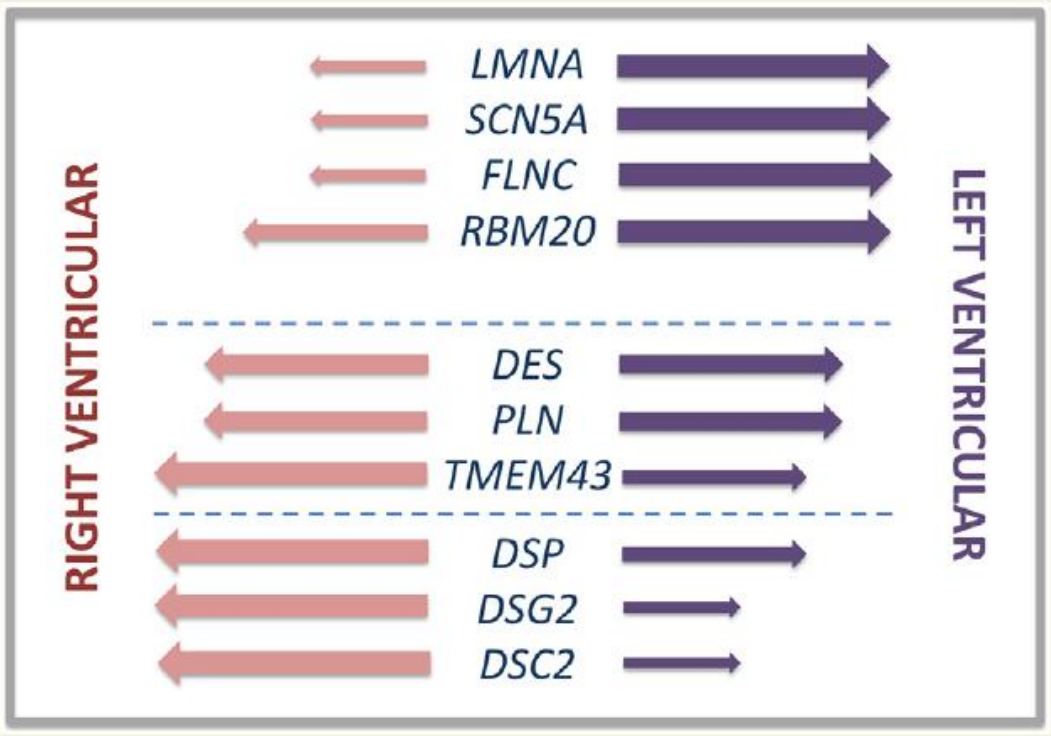


Figure 2 Genes associated with a high propensity for dilated cardiomyopathy (DCM) and ventricular arrhythmias. These arrhythmic genes included desmosomal genes that predominantly cause arrhythmogenic right ventricular cardiomyopathy (ARVC), non-desmosomal genes associated with ARVC, DCM or both, and genes that predominantly cause DCM.

Heart, Lung and Circulation (2019) **28,** 31–38

3. PROGNOSTICKÝ VÝZNAM GENETICKÉHO VYŠETŘENÍ- VZTAH K REVEZNÍ REMODELACI LKS U DKMP

Racionále: zmenšení objemu a částečné zlepšení systolické funkce LKS u pacientů s novým záchytem DKMP je spojeno s příznivou prognózou onemocnění, genetické prediktory dosud málo prozkoumány.

METHODS AND RESULTS: Patients with DCM and hypokinetic non-DCM (n=346; mean left ventricular ejection fraction, 30%) underwent genotyping for 47 DCM-associated genes in addition to extensive phenotyping. LVRR was defined as improvement of left ventricular ejection fraction >50% or ≥10% absolute increase, with cardiac dimensions (left ventricular end diastolic diameter) ≤33 mm/m^2 or ≥10% relative decrease. LVRR occurred in 180 (52%) patients after a median follow-up of 12-month optimal medical treatment. Low baseline left ventricular ejection fraction, a hypokinetic non-DCM phenotype, high systolic blood pressure, absence of a family history of DCM, female sex, absence of atrioventricular block, and treatment with β-blockers were all independent positive clinical predictors of LVRR. With the exception of *TTN*, genetic mutations were strongly associated with a lower rate of LVRR (odds ratio, 0.19 [0.09–0.42]; *P*<0.0001). *TTN* and *LMNA* were independently associated with LVRR (odds ratio, 2.49 [1.09–6.20]; *P*=0.038 and 0.11 [0.01–0.99]; *P*=0.049, respectively). Adding mutation status significantly improved discrimination (C statistics) and reclassification (integrated discrimination improvement/net reclassification index) of the clinical model predicting LVRR. Furthermore, the risk for heart failure hospitalization and cardiovascular death is lower in the LVRR patients on the long term (hazard ratio, 0.47 [0.24–0.91]; *P*=0.009 and 0.18 [0.04–0.82]; *P*=0.007, respectively), and LVRR is an independent predictor for event-free survival.

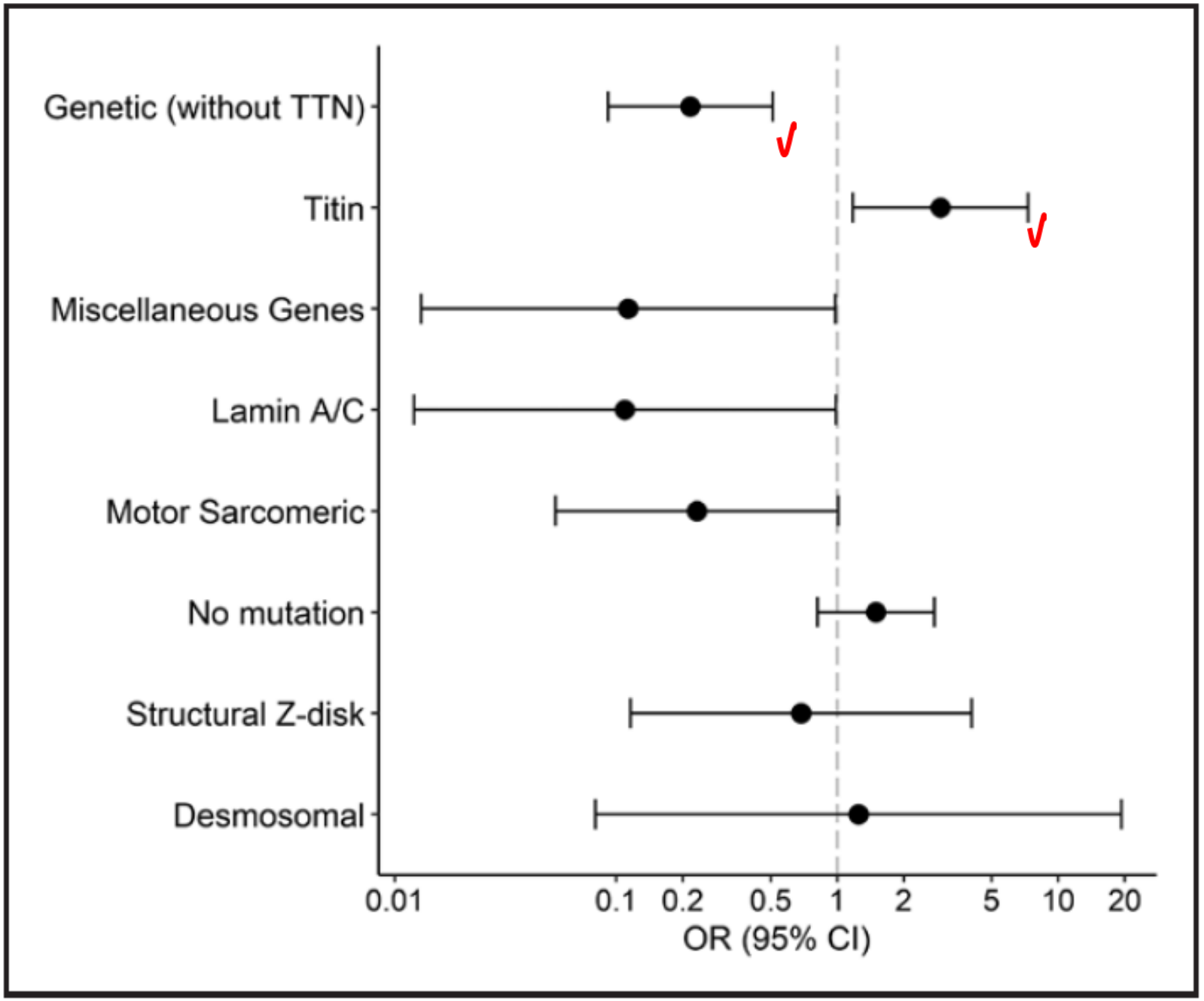


Figure 2. Association between mutation status and left ventricular reverse remodeling (LVRR) adjusted for the clinical prediction model.

Circ Heart Fail. 2018;11:e005220.

4. INTERAKCE GENOTYPU A PROSTŘEDÍ- OVLIVNĚNÍ ABUSEM ALKOHOLU

Racionále: trunkují mutace titinu byly nalezeny u pacientek s těhotenskou KMP a recentně u alkoholické KMP, obě onemocnění mají značnou reverzibilitu.

Interakce genotypu a abusu alkoholu u DKMP

METHODS The authors characterized 141 ACM cases, 716 DCM cases, and 445 healthy volunteers. The authors compared the prevalence of rare, protein-altering variants in 9 genes associated with inherited DCM. They evaluated the effect of genotype and alcohol consumption on phenotype in DCM.

RESULTS Variants in well-characterized DCM-causing genes were more prevalent in patients with ACM than control subjects (13.5% vs. 2.9%; $p = 1.2 \times 10^{-5}$), but similar between patients with ACM and DCM (19.4%; $p = 0.12$) and with a predominant burden of titin truncating variants (TTNtv) (9.9%). Separately we identified an interaction between *TTN* genotype and excess alcohol consumption in a cohort of DCM patients not meeting ACM criteria. On multivariate analysis, DCM patients with a TTNtv who consumed excess alcohol had an 8.7% absolute reduction in ejection fraction (95% confidence interval: −2.3% to −15.1%; $p < 0.007$) compared with those without TTNtv and excess alcohol consumption. The presence of TTNtv did not predict phenotype, outcome, or functional recovery on treatment in ACM patients.

CONCLUSIONS TTNtv represent a prevalent genetic predisposition for ACM, and are also associated with a worse left ventricular ejection fraction in DCM patients who consume alcohol above recommended levels. Familial evaluation and genetic testing should be considered in patients presenting with ACM. (J Am Coll Cardiol 2018;71:2293–302)

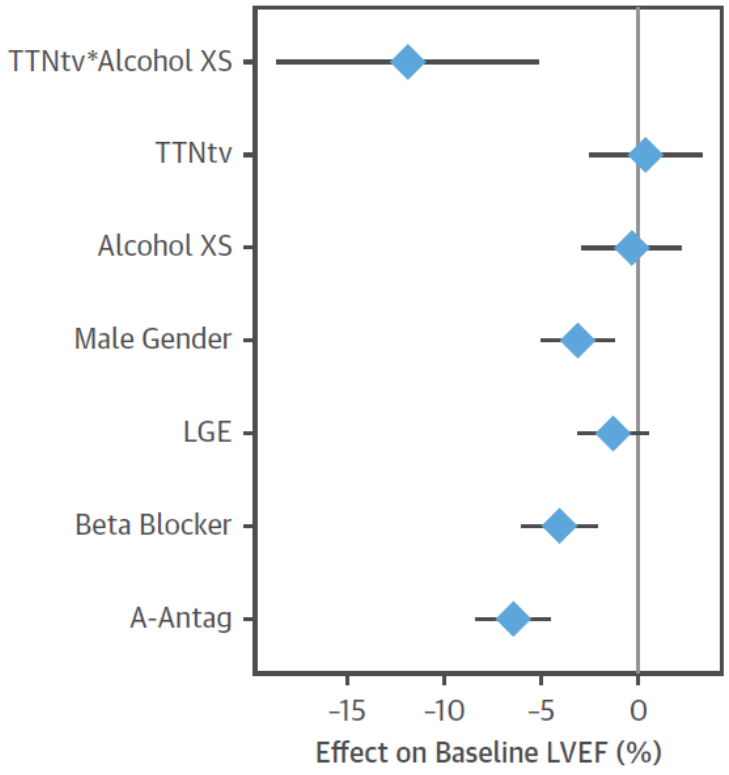
Alkoholická KMP= více než 80g alkoholu denně po dobu delší nežli 5 let

Interakce genotypu a abusu alkoholu u DKMP

TABLE 2 Burden Analysis of Rare, Protein-Altering Variants in DCM-Related Genes Between Cohorts

	ACM (n = 141)	DCM (n = 366)	Healthy Volunteer (n = 445)	*ACM vs. DCM	*ACM vs. Healthy Volunteer	*DCM vs. Healthy Volunteer
All genes	19 (13.5) (7.8%–19.1%)	71 (19.4) (15.3%–23.4%)	13 (2.9) (1.4%–4.5%)	0.12	1.2×10^{-5}	5.4×10^{-15}
TTNtv	14 (9.9) (5.0%–14.9%)	44 (12.0) (8.7%–15.4%)	3 (0.7) (0.0%–1.4%)	0.64	4.4×10^{-7}	6.4×10^{-12}
Genes other than *TTN*	6 (4.3) (0.9%–7.6%)	28 (7.7) (4.9%–10.4%)	10 (2.2) (0.9%–3.6%)	0.23	0.23	0.00035

FIGURE 2 Alcohol and TTNtv Act in Combination, and Together Are Associated With a Lower Baseline LVEF in Patients With DCM



JACC VOL. 71, NO. 20, 2018
MAY 22, 2018:2293–302

ZÁVĚR

- Podrobné zhodnocení RA a klinický screening jsou doporučeny u všech pacientů s DKMP.

- Molekulárně-genetické vyšetření je nejvýtěžnější u mladých pacientů s DKMP, a dále u familiárních a syndromických forem onemocnění.

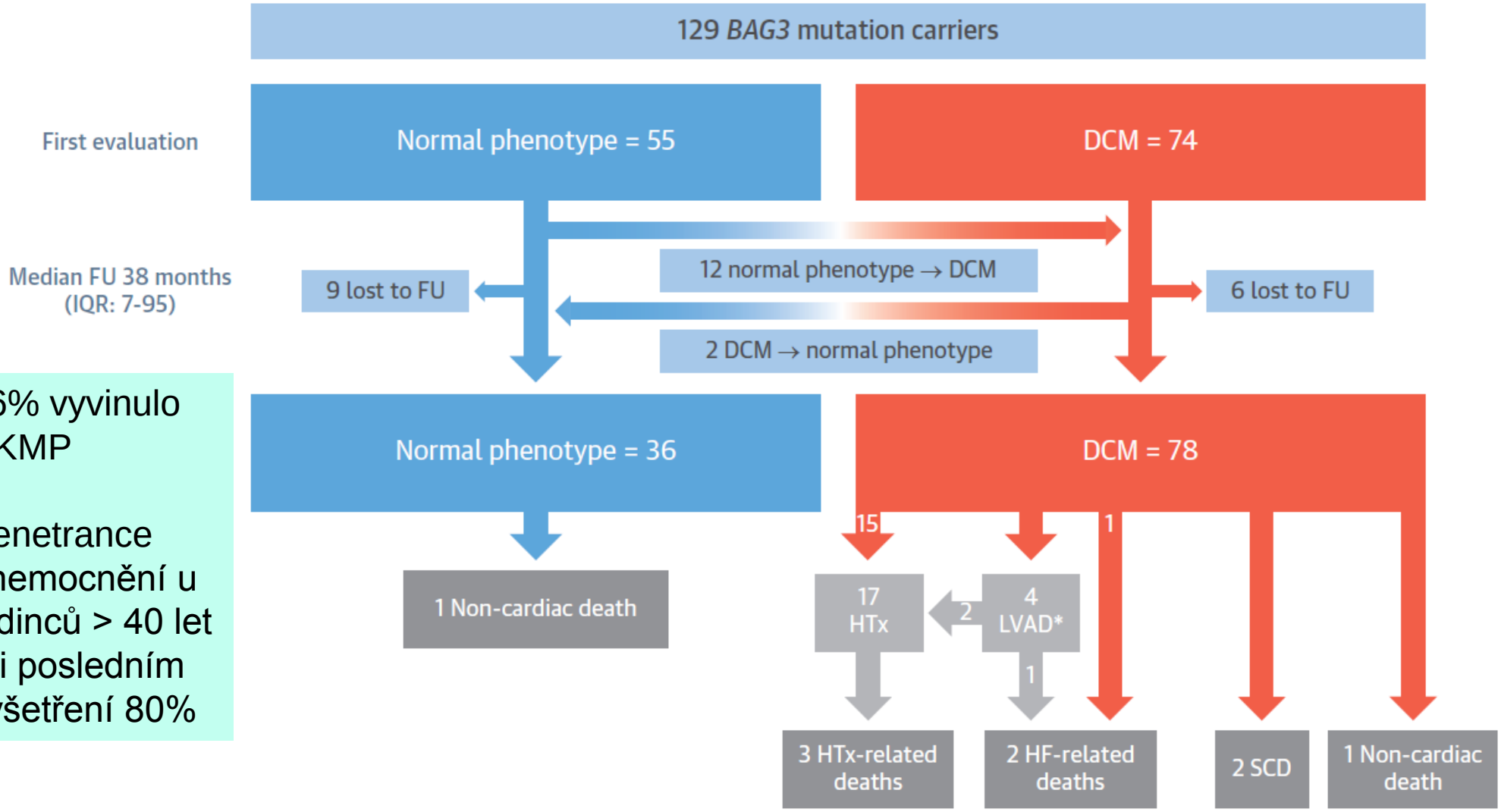
- Cílem rodinného screeningu je časná léčba postižených příbuzných v presymptomatické fázi.

- Genotypizace by mohla upřesnit arytmické riziko a předpověď reakce na léčbu u těchto nemocných.

Děkuji Vám za pozornost!

DKMP podmíněná mutací BAG3 (antiapoptotický protein)

FIGURE 1 Flowchart of Patients Included in the Study

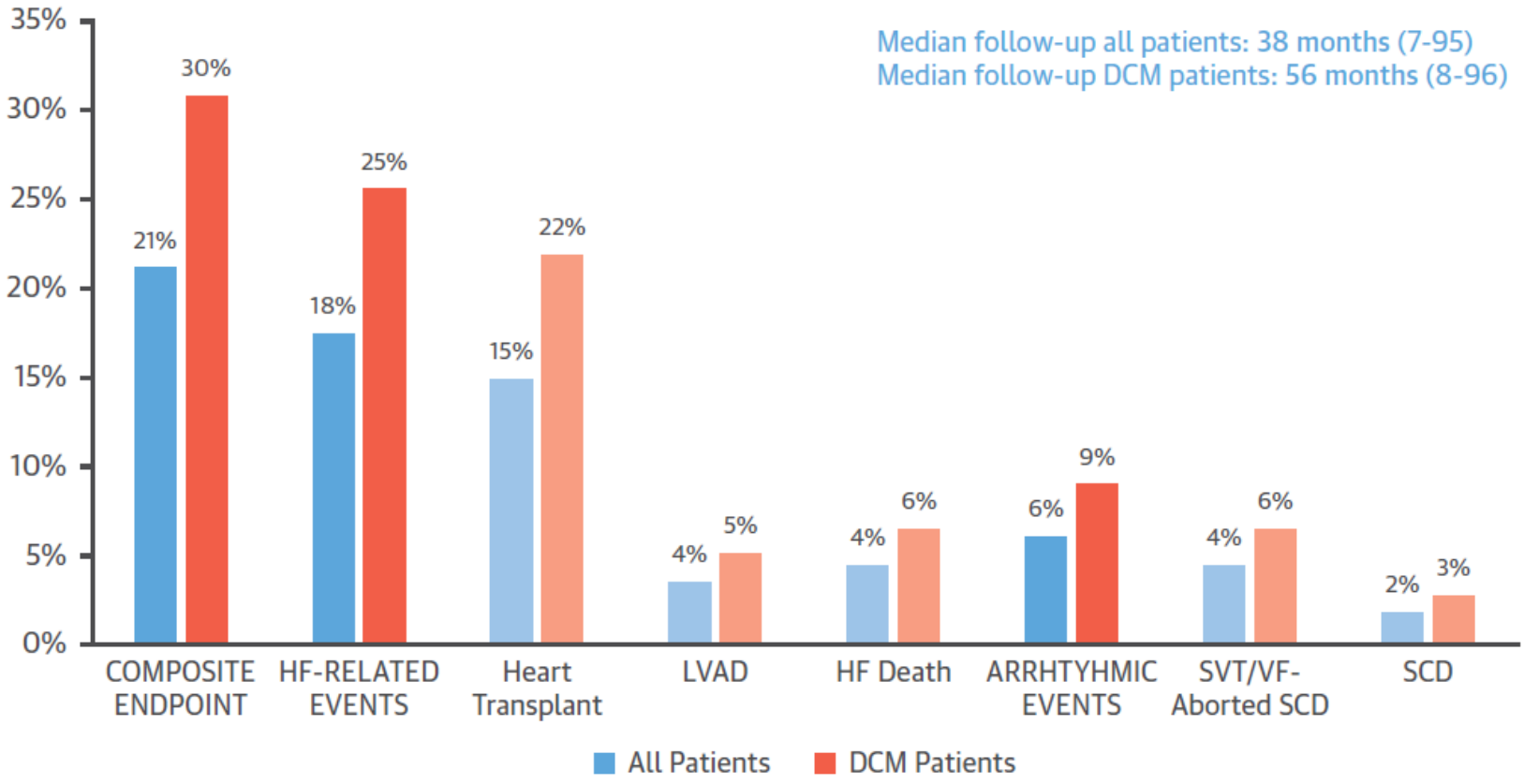


26% vyvinulo DKMP

Penetrance onemocnění u jedinců > 40 let při posledním vyšetření 80%

DKMP podmíněná mutací BAG3 (antiapoptotický protein)

FIGURE 2 Clinical Events During Follow-Up of Individuals With *BAG3* Mutation



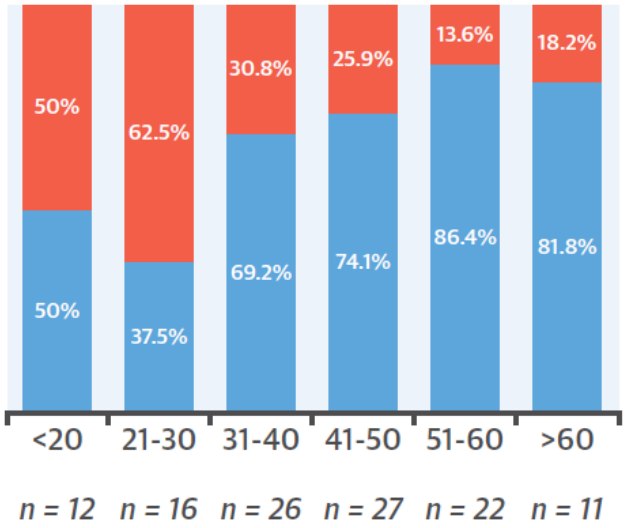
BAG3 CARDIOMYOPATHY

129 MUTATION CARRIERS

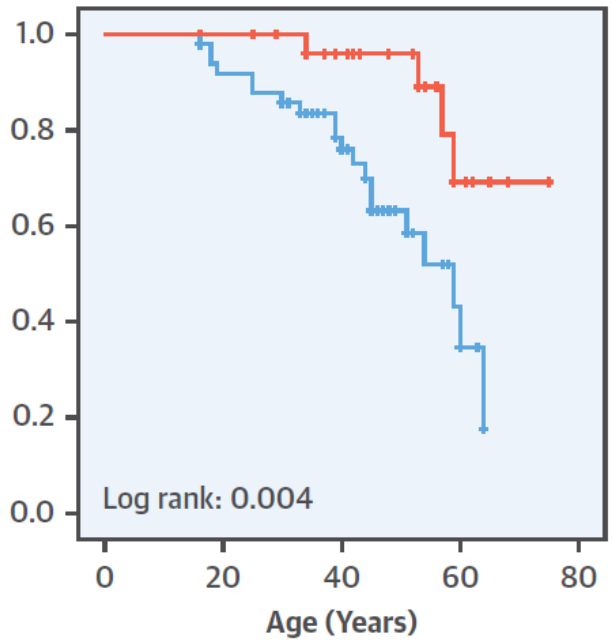
MEDIAN FOLLOW-UP 38 months*
ECG and echocardiogram at first evaluation and follow-up

PRIMARY COMPOSITE ENDPOINT:
- Heart transplant, LVAD
- SVT, appropriate ICD shock
- Cardiac death, aborted SCD

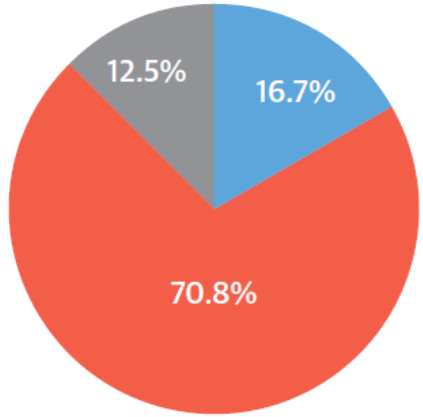
AGE DISTRIBUTION OF DCM



PRIMARY COMPOSITE ENDPOINT: Males vs. Females



5.1% EVENTS PER YEAR in DCM Patients



HIGH BUT INCOMPLETE PENETRANCE
80% in >40-Year-Old Patients

WORSE PROGNOSIS IN MALES

AGGRESSIVE COURSE
Predominance of HF Related Events

* 114 Patients With Available Follow-Up Data

DCM Phenotype Normal Phenotype

Male Female

Arrhythmic HF-Related Both

Domínguez, F. et al. J Am Coll Cardiol. 2018;72(20):2471-81.

Interakce genotypu a cytostatik o toxické KMP

BACKGROUND:
Cancer therapy-induced cardiomyopathy (CCM) is associated with cumulative drug exposures and pre-existing cardiovascular disorders. These parameters incompletely account for substantial inter-individual susceptibility to CCM. We hypothesized that rare variants in cardiomyopathy genes contribute to CCM.
METHODS:
We studied 213 CCM patients from three cohorts: retrospectively recruited adults with diverse cancers (n=99), prospectively phenotyped breast cancer adults (n=73) and prospectively phenotyped children with acute myeloid leukemia (n=41). Cardiomyopathy genes, including nine pre-specified genes were sequenced. The prevalence of rare variants was compared between CCM cohorts and The Cancer Genome Atlas (TCGA) participants (n=2053), healthy volunteers (n=445), and ancestry-matched reference population. Clinical characteristics and outcomes were assessed, stratified by genotypes. A prevalent CCM genotype was modeled in anthracycline-treated mice

Circulation. 2019 Apr 16. doi: 10.1161/CIRCULATIONAHA.118.037934.

Interakce genotypu a cytostatik u toxické KMP

RESULTS:
-CCM was diagnosed 0.4-9 years after chemotherapy; 90% of these patients received anthracyclines.
-Among nine prioritized genes CCM patients had more rare protein-altering variants than comparative cohorts (p≤1.98e-04). Titin-truncating variants (TTNtv) predominated, occurring in 7.5% CCM patients versus 1.1% TCGA participants (p=7.36e-08), 0.7% healthy volunteers (p=3.42e-06), and 0.6% reference population (p=5.87e-14).
-Adult CCM patients with TTNtv experienced more heart failure and atrial fibrillation (p=0.003) and impaired myocardial recovery (p=0.03) than those without.
-Consistent with human data, anthracycline-treated TTNtv mice and isolated TTNtv cardiomyocytes showed sustained contractile dysfunction unlike wildtype (p=0.0004 and p<0.002, respectively).
CONCLUSIONS:
Unrecognized rare variants in cardiomyopathy-associated genes, particularly TTNtv, increased the risk for CCM in children and adults, and adverse cardiac events in adults. Genotype, along with cumulative chemotherapy dosage and traditional cardiovascular risk factors improves identification of cancer patients at highest risk for CCM.

Circulation. 2019 Apr 16. doi: 10.1161/CIRCULATIONAHA.118.037934.

Doporučení pro skrínink KMP v rodině

Genetic Evaluation of Cardiomyopathy—A Heart Failure Society of America Practice Guideline

Journal of Cardiac Failure Vol. 24 No. 5 2018

Obtaining a family history of at least 3 generations, including the creation of a pedigree, is recommended for all patients with a primary cardiomyopathy.

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	A
Restrictive cardiomyopathy (RCM)	A
Cardiomyopathies with extracardiac manifestations	A
Left ventricular noncompaction (LVNC)	See Background

Clinical (phenotypic) screening for cardiomyopathy in at-risk 1st-degree relatives is recommended.

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	A
Restrictive cardiomyopathy (RCM)	A
Cardiomyopathies, overlapping, or extracardiac	A
Left ventricular noncompaction (LVNC)	See Background

Genetic testing is recommended for patients with cardiomyopathy.

4a. Genetic testing is recommended for the most clearly affected family member.

4b. Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.

4c. In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.

Cardiomyopathy Phenotype	Level of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	A
Arrhythmic right ventricular cardiomyopathy (ARVC)	A
Restrictive cardiomyopathy (RCM)	B
Cardiomyopathies associated with other extracardiac manifestations	A
Left ventricular noncompaction (LVNC)	See Background