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Progression of cardiomyopathy in patients with muscular dystrophy - a CMR-based extensive follow-up study

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Background: Becker (BMD) and Duchenne (DMD) muscular dystrophies (MD) are X-linked progressive neuromuscular disorders. Cardiac involvement with a non-ischemic, myocarditis-like pattern of left ventricular (LV) myocardial fibrosis leading to dilated cardiomyopathy is a major cause of morbidity and mortality. Cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) is increasingly used for (initial) diagnosis as well as for subsequent surveillance of cardiac disease in MD patients. However, CMR-based follow-up data are still limited in MD patients.
Methods: Between 2007 and 2016, n=112 DMD/BMD males underwent comprehensive CMR studies including (amongst others) cine- and LGE-imaging. In n=83 of these patients (31±14 years; 22% DMD and 78% BMD) at least one follow-up (FU) CMR study was performed.
Results: CMR parameters at baseline were as follow: LV-EDVi = 81±25 ml/m^2, LV-EF = 55±11%, LV-mass = 58±16 g/m^2, and n=54 (65%) MD patients were LGE-positive. After a median FU period of 6 years (range 1 to 10 years), there was an increase in LV-EDV to 87±25 ml/m^2 (p=0.004 vs. baseline), a decrease in LV-EF to 52±11% (p<0.001 vs. baseline) and in LV-mass to 55±14 g/m^2 (p=0.024 vs. baseline). The proportion of MD patients with an impaired LV function (LV-EF <55%) increased from 45 to 49% (p=NS) and those with a LV-EF ≤35% from 6 to 8% (p=NS). At FU, the prevalence of LGE-positive MD patients significantly increased to 78% (p=0.08 vs. baseline). In the n=54 LGE-positive MD patients at baseline, median LGE extent (%LV-mass) increased from 9% (1 to 44%) to 11% (1 to 40%) (p<0.001) and the number of LGE-positive segments increased from 4 (1 to 13) to 7 (1 to 16) (p<0.001). The prevalence of a transmural pattern of LGE increased from 28% to 46% in these patients (p=0.023). Those n=11 initially LGE-negative MD that developed LGE at follow-up showed a median LGE extent of 2% (0.5 to 15) and 3 (1 to 9) segments, whereas none of them presented a transmural LGE pattern.
Conclusion: MD patients suffer from progressive cardiomyopathy that can be non-invasively assessed by CMR and that is characterized by a progressive increase in LGE prevalence and extent as well as a concurrent decline in LV-EF and LV-mass. This is the first follow-up study using CMR that examined the cardiac disease course in MD patients for up to 10 years.

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Clinical characteristics and natural history of dilated cardiomyopathy due to BAG3 mutations

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Background: The BAG3 (BLC2-associated athanogene 3) gene codifies for an anti-apoptotic protein that localizes on the sarcomere Z-disc. BAG3 mutations have been related with dilated cardiomyopathy (DCM), but only a small number of cases have been reported.
Objectives: This study sought to describe the phenotype and natural history characteristics in a large multicentric cohort of DCM caused by BAG3 mutations.
Methods: Clinical, electrocardiographic and echocardiographic data from 133 BAG3 mutation carriers (60.2% males, 36.2±15.8 years) followed at 21 European centers were included. Localization of BAG3 in cardiac tissue was analyzed in patients with truncating BAG3 mutations using immunohistochemistry.
Results: DCM penetrance among BAG3 mutation carriers at first evaluation was 54.8%. After a median follow-up of 33 months (IQR: 6–91.5), 73.7% of patients exhibited DCM with 46.8% of subjects who initially did not show DCM. Age at disease onset was earlier in men than in women (34.7±14.7 vs 43.0±14.02; p=0.01). The incidence of the composite endpoint of death, left ventricular assist device (LVAD), heart transplantation (HTx), aborted sudden cardiac death (SCD) and appropriate ICD shock was 4.2% per year in the entire cohort and 7.7% per year among individuals with overt DCM at first evaluation. Age at DCM onset, left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF) and non-sustained ventricular tachycardia (NSVT) were related with the composite endpoint in BAG3 mutation carriers (Figure 1). Only 1 patient (0.8%) exhibited muscular involment. Myocardial tissue from BAG3 mutation carriers with overt DCM showed myofibrillar disarray and relocation of protein BAG3 outside sarcomeric Z discs.

	No serious clinical events during follow-up (n=92)	Serious clinical events during follow-up (n=24)	p
Male sex (%)	73.2	26.8	0.13
Female sex (%)	85.1	14.9	
Missense mutation (%)	17.4	23.1	0.57
No missense mutation*(%)	82.6	76.9	
Age at first evaluation	40.1 ± 15.0	34.6 ± 15.7	0.13
QRS width (ms) on 1st ECG	93.9 ± 17.6	96.6 ± 18.5	0.59
Negative T waves on 1st ECG (%)	14.3	33.3	0.054
LVEDD (mm) on 1st echo	56.8 ± 9.1	65.5 ± 10.9	<0.001
LVEF (%) on 1st echo	48.3 ± 14.0	27.9 ± 14.5	<0.001
TAPSE (mm) on 1st echo	20.8 ± 4.3	17.5 ± 2.7	0.14
NSVT on Holter monitor (%)	23.3	62.5	0.03
CK (UI/L)	102.1 ± 59.0	117.5 ± 119.7	0.48

CK: Creatin kinase, LVEDD: Left ventricular end diastolic diameter, LVEF: Left ventricular ejection fraction.
*: Non-sense, insertion-deletion and splice mutations
BAG3 mutation carriers: Event predictors

Conclusions: DCM caused by mutations in BAG3 is characterized by an earlier onset in males, a high but incomplete penetrance at 40 years of age and a poor prognosis. Its phenotype is cardiac specific, with a predominance of heart failure complications over arrhythmias. A younger age of DCM onset, increased LVEDD, reduced LVEF and the presence of NSVT are related with an adverse prognosis during follow-up in patients with this DCM subtype.

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Innovative approach for risk stratification of LMNA-related cardiomyopathy: results from an integrated cardiological and neurological 10-year follow-up multicentre study

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Background: Mutations in the LMNA gene have been associated with neuromuscular (N) and cardiac (C) manifestations, with possible overlapping phenotypes. However, nowadays risk stratification of sudden death and heart failure (HF) in LMNA-related cardiomyopathy is based on cardiological predictors only.
Purpose: We present results from a multicentre registry of LMNA mutation carriers undergone a complete integrated C and N evaluation, with the longest follow-up published so far.
Methods: 164 LMNA mutation carriers (median age 38 y; 51.2% females) were enrolled from 13 referral centers. All of them underwent a combined C and N assessment at the time of enrollment and 2/y for 10 y median FU, including ECG, Holter monitoring, and imaging data. Further detailed clinical information were collected retrospectively. The purpose of the study was to describe natural history of the disease and to stratify cardiac risk based on an innovative multispecialistic approach.
Results: Disease onset was more commonly N (53% of cases, median age 25y), preceding C phenotype by 11y. However, by the end of FU, 90% of the population had signs of electrical and -later- structural heart disease. Overall, 10 patients (6.1%) died, 14 (8.5%) underwent heart transplantation (HTx), and 32 (19.5%) experienced malignant ventricular arrhythmias (MVA). Furthermore, 15 and 6 patients, respectively, showed gait loss and respiratory failure from neuromuscular disease. Multivariable analysis showed three independent predictors for the composite endpoint of cardiac death, HTx and MVA: nonsustained ventricular tachycardias (HR 3.98, 95% CI 1.72–9.21, p=0.001), baseline left ventricular ejection fraction <50% (HR 3.83, 95% CI 1.75–8.38, p=0.001) and tendon retractions (TR) in skeletal muscles (HR 4.22, 95% CI 1.70–10.47, p=0.002). TRs predicted outcome independently of number, site, timing of occurrence and specific myopathy (LGMD, EDMD, LCMD, mild phenotypes). Non-missense mutations were associated only to end-stage HF, but not to MVA. Further remarkable findings emerged from analysis of subgroups: 1) in spite of a better global outcome, asymptomatic relatives were not free from significant disease (with MVA or end-stage HF observed in 4 cases); 2) patients with combined N+C involvement were younger

(median 26 vs. 35y, p<0.001) and more symptomatic, but had no differences in echocardiographic parameters as compared to those with isolated C disease (all p=n.s); 3) cardiac structural phenotype showed worse outcome and significantly higher MVA occurrence than pure electrical disease (32% vs. 4%, p<0.001); 4) overall, optimal treatment including betablockers, ACE-inhibitors and CRT had no considerable impact on prognosis (all p=n.s).
Conclusion: This large collaborative study showed that an integrated C and N evaluation allows for a significant improvement in the knowledge of both natural history of laminopathies and risk stratification in LMNA-associated heart disease.

COMPLEX DECISIONS IN CORONARY INTERVENTIONS

P3171
Impact of untreated coronary artery disease after primary percutaneous coronary intervention on two years clinical outcome: the residual added index

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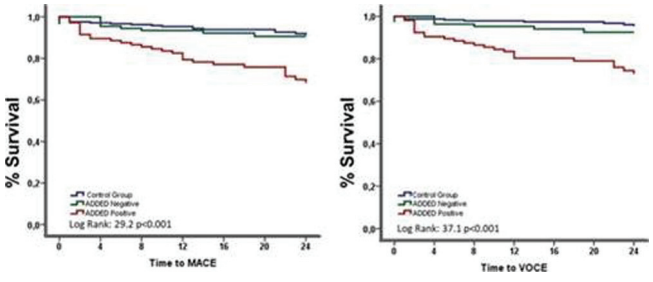
Background: Incomplete revascularization after PCI is common, particularly in patients presenting with acute coronary syndromes, and it is associated with a worse prognosis as compared with complete revascularization. In patients presenting with STEMI and multivessel disease, a FFR-based complete revascularization significantly reduces the risk of future events. The Added index, namely the ratio between minimal lumen diameter (MLD) and Duke Jeopardy Score (DJS), showed high accuracy in predicting functionally significant coronary artery stenosis with a cutoff value of 2.23.
Purpose: The aim of the present study was to investigate the prognostic value of the residual Added Index after primary PCI (pPCI) in patients presenting with STEMI and intermediate non-culprit stenosis.
Methods: We included 605 STEMI patients treated with successful pPCI. Patients with previous coronary artery bypass grafts (CABG) or presenting with cardiogenic shock were excluded. Patients were divided into 3 groups: 1) Patients without any residual coronary artery stenosis (n=321, Control group); 2) Patients with at least one residual coronary artery stenosis with a residual ADDED index lower than 2.23 (n=145, ADDED Negative group); 3) Patients with at least one residual coronary artery stenosis with a residual ADDED index equal to or higher than 2.23 (n=139, ADDED Positive group). Primary end points were: 1) major adverse cardiac event (MACE), defined as overall death, myocardial infarction, repeated revascularizations; 2) non-target vessel oriented adverse cardiac event (VOCE), defined as overall death, non-target vessel related myocardial infarction and non-target vessel related urgent or not urgent revascularizations.
Results: Patients included in the ADDED Positive group were older with higher prevalence of diabetes mellitus, hypertension and peripheral artery disease as compared with either Control group and ADDED Negative group. In addition, pPCI of the left anterior coronary artery was more often performed in both Control and ADDED Negative groups as compared with ADDED Positive group in which pPCI was more often performed in the right coronary artery. Follow-up was obtained in 77% of patients at a median of 24 months (14–36 months). Figure 1 shows the Kaplan Mayer analysis for both MACE and VOCE. At multivariate analysis, MACE rate was significantly higher in the ADDED Positive group as compared with ADDED Negative and Control Group (respectively, 29 [27%] vs 9 [8%] vs 18 [7%], adjusted hazard ratio 2.43 [1.38–4.29], p=0.002]) as well as the rate of VOCE (respectively, 25 [23%] vs 7 [6%] vs 9 [4%], adjusted hazard ratio 4.87 [2.17–10.00], p<0.001]).



Conclusions: After pPCI, deferring treatment of non-culprit lesions with a positive residual ADDED index value is associated with a significant higher risk of cardiovascular events at 2 years.

P3172
Non-uniform temporal evolution of fractional flow reserve (FFR) in intermediate coronary lesions: what matters?

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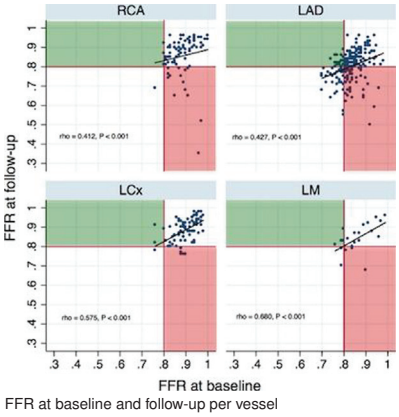
Background/Introduction: To explore if FFR evolves uniformly over time in coronary lesions according to their location and their baseline hemodynamic status.
Methods: A retrospective, single-center analysis of all coronary stenoses that were functionally evaluated by consecutive FFR measurements at two time points at least six months apart was performed. Stenoses in vessels that had been revascularized by percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG) between the two time points were excluded.
Results: 414 stenoses from 331 patients were analyzed with a time interval between the FFR measurements of 24 (17, 37) months. FFR follow-up was significantly lower than FFR baseline [0.83 (0.79, 0.90) versus 0.86 (0.82, 0.90), P<0.0001] and the overall dFFR was -0.007 (-0.028, 0.010) per year. In mixed effect repeated measures analysis, only lesion location had an independent correlation with FFR values after adjusting for multiple confounders. The rate of FFR change was not uniform for all stenosis, with faster progression for LAD lesions. The stenoses with higher FFR baseline values deteriorated more rapidly as compared to those with lower FFR baseline values. The rates of change for stenoses with FFR baseline 0.70–0.79, 0.80–0.89 and 0.90–1.00 were 0.010 (-0.011, 0.022), -0.005 (-0.026, 0.010) and -0.018 (-0.035, 0.013) respectively, with P=0.0001 for the Kruskall-Wallis test.



FFR at baseline and follow-up per vessel

Conclusions: Faster functional atherosclerosis progression (lower FFR values) is observed with LAD stenoses. From a practical standpoint, our data suggest to systemically re-assess with FFR intermediate LAD lesions at the occasion of a repeat angiogram. Similarly, progression (or regression) rate of FFR also differs according to baseline values; lesions that have the higher FFR baseline (in the range of 0.9–1.00) deteriorate faster.

P3173
Anatomic complexity and lipid plaque burden in NSTE-ACS smoker patients with or without COPD: insights from the SCAP trial

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Background: The effects of COPD on coronary artery lesions are unknown. The Screening for COPD in ACS patients (SCAP) trial enrolled acute coronary syndrome (ACS) patients with smoking habit without known COPD to detect undiagnosed COPD (UCOPD).
Purpose: To evaluate the anatomic complexity (Syntax score) and plaque lipid core burden index (LCBI through near infrared spectroscopy (NIRS)) in patients hospitalized for no ST-elevated (NSTE)-ACS enrolled in the SCAP trial.
Methods: The SCAP trial study protocol mandated to perform Syntax score and suggested to perform NIRS in the culprit lesion and at least in one non-culprit lesion, in all patients presenting with NSTE-ACS. LCBI and Max LCBI 4 mm were calculated in all analyzed vessels by two independent investigators.
Results: SCAP trial enrolled 78 patients with NSTE-ACS. NIRS was performed in 65 patients on a total of 151 vessels. The number of diseased vessels and the Syntax score were comparable between the two groups (UCOPD and no COPD). The LCBI and max LCBI 4mm were significantly higher in the UCOPD group. The same result was found in culprit and in non-culprit coronary arteries (LCBI culprit: UCOPD 119 [102–146]; no COPD 71 [50–119], p=0.01; LCBI non culprit: UCOPD 111 [69–144]; no COPD 77 [46–104], p=0.002; LCBI max 4 mm culprit: UCOPD 424 [399–464]; no COPD 286 [178–385], p<0.001; LCBI max 4 mm non-culprit: UCOPD 337 [286–408]; no COPD 233 [151–333], p<0.001). The number of vessel with max LCBI 4 mm>400 was significantly higher in the UCOPD group

Study results

	All (Patients n=65, Vessels n=151)	UCOPD (Patients n=18, Vessels n=42)	No COPD (Patients n=47, Vessels n=109)	
NSTEMI, no.	43 (66)	13 (72)	30 (64)	0.4
Number of diseased vessels	2 [1–2]	2 [1–2]	2 [1–2]	0.8
Syntax score	13 [5–23.5]	13.5 [5.5–24]	12.5 [5–24.5]	0.7
LCBI	84 [56–120]	117 [70–144]	74 [50–107]	<0.001
Max LCBI 4 mm	298 [198–401]	406 [302–430]	261 [176–350]	<0.001

UCOPD: undiagnosed chronic obstructive pulmonary disease. NSTEMI: no ST-elevated myocardial infarction. LCBI: lipid core burden index.