5163

Predictors of adverse cardiovascular events in patients with truncating variants in the filamin c (flnc) gene

M. Akhtar[1], D. Rangel-Sousa[2], J. Palomino-Doza[3], X. Arana Achaga[4], Z. Bilinska[5], E. Zamarreno Golvano[6], V. Climent[7], M. Navarro Penalver[8], R. Barriales-Villa[9], P. Charron[10], R. Yotti[11], E. Zorio[12], J. Jimenez-Jaimez[13], P. Garcia-Pavia[14], P.M. Elliott[2]

[1]Barts Health NHS Trust, London, United Kingdom; [2]University College London, London, United Kingdom; [3]University Hospital 12 de Octubre, Madrid, Spain; [4]University Hospital Donostia, Donostia-San Sebastian, Spain; [5]The Cardinal Stefan Wyszynski Institute of Cardiology, Warsaw, Poland; [6]Hospital de Basurto, Bilbao, Spain; [7]General University Hospital of Alicante, Alicante, Spain; [8]Hospital Universitario Virgen Arrixaca, Murcia, Spain; [9]Instituto de Investigación Biomédica de A Coruña (INIBIC), A Coruna, Spain; [10]Hospital Pitie-Salpetriere, Paris, France; [11]University Hospital Gregorio Maranon, Madrid, Spain; [12]Hospital Universitario y Politécnico La Fe, Valencia, Spain; [13]University Hospital Virgen de las Nieves, Granada, Spain; [14]Hospital Universitario Puerta de Hierro, Madrid, Spain

On behalf of European Genetic Cardiomyopathies Initiative Investigators

Funding Acknowledgement: NIHR Biomedical Research Centre; Instituto de Salud Carlos III; DETECTIN-HF project; Wellcome Trust;CIBERCV; EU Regional Development Fund; FEDER.

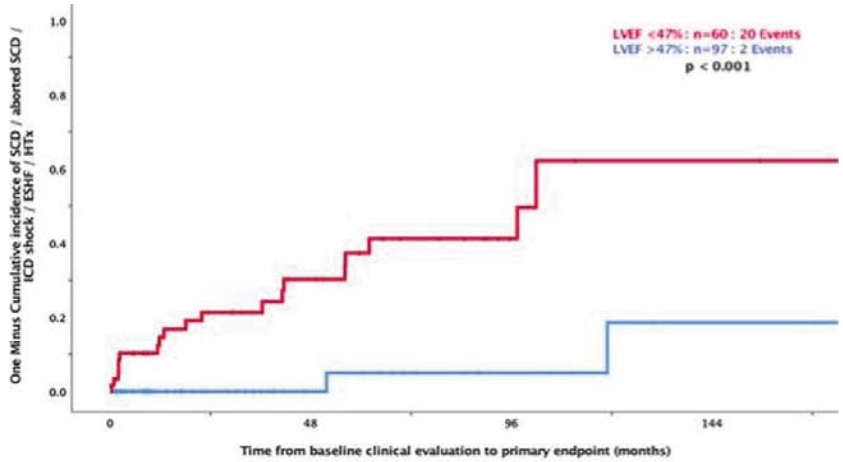
Background: Truncating variants in Filamin C (FLNCtv) are associated with arrhythmogenic (AC) and dilated cardiomyopathies (DCM). Affected patients are reported to demonstrate a high incidence of arrhythmic and heart-failure related cardiovascular events. The aim of this study was to determine factors that predict adverse events in mutation carriers.

Methods: The study cohort comprised 168 FLNCtv carriers followed at 19 European centres. Baseline and longitudinal follow-up clinical data were collected. The primary endpoint was a composite of sudden cardiac death (SCD), aborted SCD, appropriate implantable cardioverter-defibrillator (ICD) shock, cardiac transplantation (HTx) and mortality from end-stage heart failure (ESHF).

Results: 47 different pathogenic or likely-pathogenic FLNCtv were identified in 60 unrelated probands. In those with baseline and longitudinal data (160 patients; 57 probands), 114 (71.3%) patients exhibited evidence of cardiac disease at initial evaluation. Gene penetrance was 85% by the age of 40 years. During a median follow-up of 1.5 years (IQR 4.1), 24 individuals (15%) reached the primary endpoint – 16 arrhythmic (SCD/aborted SCD/ICD shock) and 8 heart failure (ESHF/HTx) related-events. Univariable predictors at baseline evaluation of the composite primary endpoint included proband status (HR 4.0, 95% CI: 1.5–10.9, p=0.01), symptoms of dyspnoea (HR 2.8, 95% CI: 1.2–6.4, p=0.02), LV systolic dysfunction (LVSD) (HR 12.4, 95% CI: 2.9–53.2, p=0.001), frequent ventricular ectopy (VE>500) on 24-hour Holter (HR 9.3, 95% CI: 1.2–74.7, p=0.04) and the presence of late gadolinium enhancement on CMR (HR 8.9, 95% CI: 1.2–68.5, p=0.04).

Multivariable analysis identified LVSD (LVEF <50%) at baseline as an independent predictor of the primary endpoint with a hazard ratio of 8.6 (95% CI: 1.8–41.5, p=0.007). ROC analysis using LV systolic dysfunction to predict the primary endpoint demonstrated an area under the curve of 0.84 (95% CI: 0.76–0.91, p<0.001) and identified an optimal LVEF "cut-off" of 47% for predicting adverse events with a Youden's index of 0.61 (sensitivity 0.91; specificity 0.70).

Conclusions: LVSD is associated with an over 8-fold increase in the hazard of a primary endpoint event in FLNCtv gene carriers indicating that these patients should be considered for implantable cardioverter-defibrillator (ICD) implantation, optimal heart failure medical therapy and close clinical follow-up.



Number at Risk	0-24 months	24-48 months	48-72 months	72-96 months	96+ months
LVEF ≥ 47%	97	38	20	13	9
LVEF < 47%	60	34	22	13	7

Kaplan-Meier plot to demonstrate freedom