

**Table 2** (Continued)

Parameters assessed in forced spirometry, 6 minute walk test, and ergospirometry, before and after the cardiopulmonary rehabilitation program

	Before CR	After CR	P
PedsQL score, parent-proxy	1700 (1550-1900)	1775 (1175-2075)	.144
Number of NSS-36 questionnaires, young adults	14	15	
SF-36 score, young adults	103 (94-110)	103 (87-115)	.779

AT, anaerobic threshold; CR, cardiopulmonary rehabilitation; DBP, diastolic blood pressure; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, heart rate; O<sub>2</sub>P, oxygen pulse; OUES, oxygen uptake efficiency slope; PedsQL, Pediatric Quality of Life Inventory Cardiac Module, version 4.0 used in our study for pediatric patients (age 8 to 18 years) and their parents; PetCO<sub>2</sub>, end-tidal partial pressure of CO<sub>2</sub>; SBP, systolic blood pressure; SF-36, Short Form Health Survey; VCO<sub>2</sub>, carbon dioxide production; VE, minute ventilation; VO<sub>2</sub>, oxygen uptake; VR, ventilatory reserve.

\* Patient #9 was excluded from this analysis due to Fontan circulation (this parameter is interpreted differently between cyanotic and noncyanotic patients).

group. Implementation of the program was a challenge, as difficulties were encountered for administration to understand that CR should focus on comprehensive prevention units open to all heart diseases, rather than only coronary patients. We show that, despite these difficulties, CR could be a cost-effective tool capable of improving functional capacity and quality of life in complex CHDs. In our experience, CR has helped to support our patients and their families and enabled them to understand their limits and to encourage improvements in their functional capacity.

## FUNDING

Biomedicine, health management, and social and health care research project funded by the Regional Health Agency of Castilla y León (G 1369/A/16) and the CIBERCV, Carlos III Health Institute, Ministry of Science, Innovation, and Universities.

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Available online 3 March 2020

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<https://doi.org/10.1016/j.rec.2019.12.007>  
1885–5857/

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## Truncating titin variants in dilated cardiomyopathy: not only LVEF recovery, but also maintenance



### Miocardopatía dilatada asociada a variantes tipo truncamiento en titina: no solo recuperación de la FEVI, también mantenimiento

#### To the Editor,

Truncating titin variants (TTNtv) are the main genetic cause of dilated cardiomyopathy (DCM).<sup>1</sup> These variants have been associated with a mild and treatable form of DCM<sup>2</sup> (the need for a ‘second hit’ such as chemotherapy or alcohol abuse has been even suggested),<sup>3</sup> but also with an increased risk of arrhythmias/sudden death.<sup>4,5</sup> The

latter has aroused concerns about a lower threshold for defibrillator implantation, as practiced in other genetic forms of DCM.

The titin (TTN) gene encodes 364 exons that undergo alternative splicing to produce different isoforms. In the adult myocardium, 2 major TTN isoforms, N2BA and N2B, are mainly expressed. Most of truncating TTN variants affect these cardiac TTN isoforms, being predominantly located at the A-band.

We present a retrospective single referral-center cohort study exploring the phenotype and prognosis of TTNtv-DCM patients compared with a well-defined control group composed of carriers of variants in other DCM-related genes.

We selected 129 adult patients with DCM/hypokinetic nondilated cardiomyopathy and genetic testing. Of these, 47 tested positive (ie, pathogenic or likely pathogenic variant according to the American College of Medical Genetics and Genomics guidelines), 56 negative,

**Table 1**  
Demographic and clinical characteristics

	Global N = 45	TTN N = 23	Non-TTN N = 22	P
Female sex, %	18 (40)	11 (47)	7 (32)	.27
Age at diagnosis	48 ± 16	53 ± 16	43 ± 13	.02*
Follow-up	62 [22-131]	75 [22-135]	54 [21-124]	.67
NYHA ≥ 3 baseline	24 (53)	12 (52)	12 (55)	.87
Initial LVEF	28 [21-37]	28 [20-37]	26 [21-36]	.78
Hypertension	13 (29)	8 (35)	5 (23)	.37
Dyslipidemia	12 (27)	10 (44)	2 (9)	<.01*
Diabetes mellitus	2 (4.4)	2 (9)	0	
Coronary disease	3 (14)	3 (7)	0	
Chronic kidney disease	7 (16)	4 (17)	3 (14)	.72
Beta-blockers	44 (98)	23 (100)	21 (96)	.30
ACEI/ARBs	44(98)	22(96)	22 (100)	.32
MRA	34 (76)	17 (74)	17 (77)	.79
ARNI	13 (29)	4 (17)	9 (41)	.08
OMT	45 (98)	22 (96)	21 (96)	.97
Conduction abnormalities, %	28 (62)	11 (47)	17 (77)	.04*
LBBB, %	15 (33)	5 (21)	10 (45)	.09
CMRI performed	22 (49)	10 (44)	12 (55)	
% LGE	10 (46)	4 (40)	6 (50)	.61
CRT	12 (27)	4 (17)	8 (38)	.12
% bVP	99	97.5	99	
LVEF after CRT	15 ± 18	21.25 ± 13	11.9 ± 21	.43
ICD	18 (39)	5 (22)	13 (59)	.01*
Primary prevention	11	4	7	
Secondary prevention	7	1	6	
LTA	11 (25)	2 (10)	9 (41)	.02*
Total deaths	3	1	2	
Cardiac cause	2	0	2	

ACEI, angiotensin converting enzyme inhibitor; ARBs, angiotensin receptor blockers; ARNI, angiotensin II receptor blocker neprilysin inhibitor; bVP, biventricular pacing; CMRI, cardiac magnetic resonance imaging; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LTA, life-threatening arrhythmias; LVEF, left ventricle ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; OMT, optimal medical therapies; TTN, titin.

Data are expressed as No. (%), mean ± standard deviation, or median [interquartile range].

\* A P value of ≤ .05 was used as a cutoff for statistical significance.

and 26 inconclusive. A total of 2 double pathogenic variant-carriers were excluded, with a final result of 45 patients: 19 TTNtv-probands, 4 phenotype-positive relatives, and 22 non-TTN probands.

For comparisons, the sample was divided into TTNtv patients (probands and phenotype-positive relatives, n = 23) and non-TTN patients (n = 22).

Demographic and clinical characteristics are shown in [table 1](#).

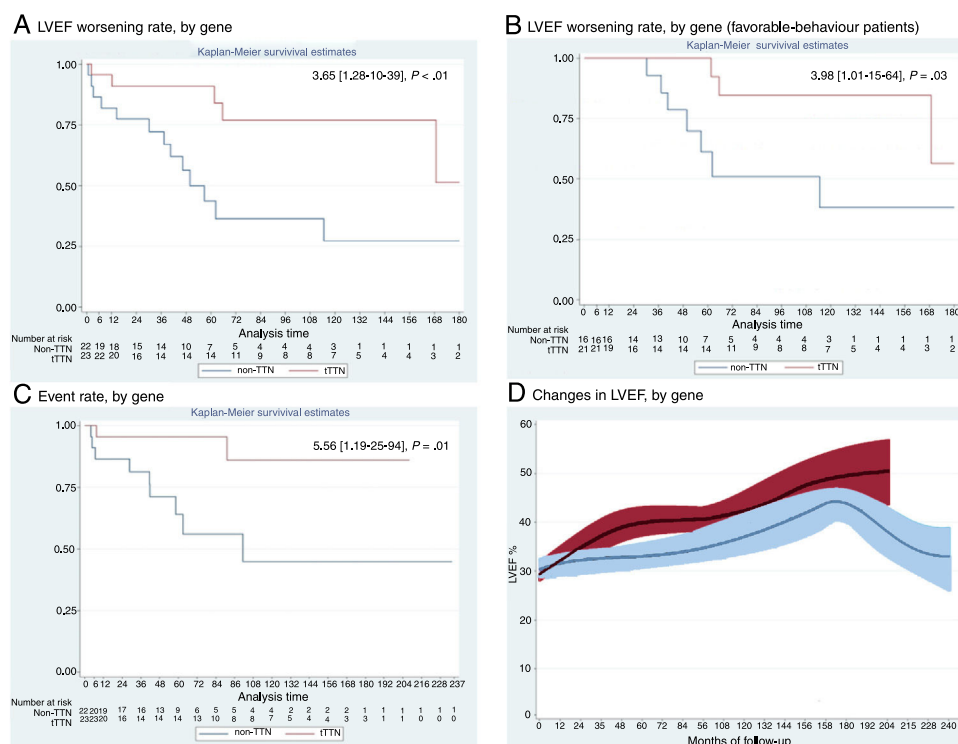
In terms of left ventricular ejection fraction (LVEF) after diagnosis and treatment, 2 possible scenarios were established: *a*) favorable behavior, in patients with a significant LVEF increase (at least 10% increase and LVEF > 30% after improvement was achieved, or patients with their first 2 LVEF values above 40%); and *b*) unfavorable behavior, if no favorable behavior as described was present.

The primary endpoint was LVEF worsening. Time of worsening was defined as LVEF < 40%, or at least 10% below the best value of each favorable-behavior patient. In unfavorable-behavior patients, time of worsening was established at the second transthoracic echocardiogram. During a median of 62 months of follow-up, non-TTN patients showed a 3.6-fold risk of LVEF worsening compared with TTNtv patients (1.28-10.39, *P* < .01; [figure 1A](#)). When we

analyzed favorable patients only (82%; 91% TTNtv vs 72% non-TTN), the differences persisted: non-TTN patients showed a 3.98-fold risk of worsening (1.01-15.64, *P* = .03; [figure 1B](#)). Time to LVEF worsening was clearly different in both groups: at 5 years of follow-up, LVEF was maintained in all favorable-behavior TTNtv patients and in only 63% of non-TTN (favorable) patients.

Secondary endpoints included: *a*) composite clinical endpoint: non-TTN patients showed a 5.56-fold risk of death, heart transplant, or left ventricular assist device (1.19-25.94, *P* = .01; [figure 1C](#)); and *b*) the presence of a significant increase in LVEF after diagnosis and treatment. LVEF improved in most patients (73% globally; 83% TTNtv vs 64% non-TTN, *P* = .15). LVEF trends were represented by Loess curves for gene subgroups and were analyzed using a linear mixed model for repeated measurements, with a statistically significant difference (*P* < .05) between them ([figure 1D](#)).

Unlike previous works, we found no significant differences in LVEF recovery between TTNtv and non-TTN patients. Although this may be due to the sample size, our more restrictive definition could also have played a role. We established LVEF improvement as an exclusively structural endpoint, and only considered increases of



**Figure 1.** Outcomes in TTNtv dilated cardiomyopathy. TTNtv in red, non-TTN in blue. Survival analysis of: A: LVEF worsening; B: LVEF worsening in favorable-behavior patients, and C: major events (death, heart transplant, or left ventricular assist device implantation). D: Changes in LVEF, by gene. For LVEF worsening analysis, outliers were excluded, delimiting follow-up in 180 months. LVEF, left ventricular ejection fraction; TTNtv, truncating titin variants.

more than 10% if the final LVEF was above 30%. In our opinion, this 30% threshold is necessary because some LVEF changes in the severely depressed area might not be clinically relevant.

Moreover, we did not compare TTNtv-DCM with idiopathic DCM. This hodgepodge term could distort results when aiming to correlate a particular genotype with phenotypic manifestations. A comparison to a well-defined control group, comprising other genetic-confirmed DCM cases, have been preferred.

Equally, we did not observe that TTNtv-DCM patients had a milder initial form: our patients had similar LVEF (28 in TTNtv vs 26) and New York Heart Association functional class at diagnosis (52% of patients above New York Heart Association II vs 55%, respectively). However, we did observe that, under optimal medical treatment, patients with TTNtv-DCM were significantly more likely to maintain the LVEF recovery achieved, which, to the best of our knowledge, has not been previously described.

A compensated-state myocardium hypothesis, intolerant to further stress, has been proposed, relating the etiopathogenesis of TTNtv-DCM to nonsense-mediated decay.<sup>6</sup> It also seems plausible that the profile of TTN isoform expression changes in the myocardium under altered charge conditions. The loss of an allele of the stiffer N2B isoform might affect the expression ratio and, as a consequence, myocardium compliance properties, in the same way as medical treatment might be a key factor to prevent TTNtv myocardium from damage.

All these data depict DCM associated with TTNtv not as a milder form of the disease, but as a more malleable entity, with a more sustained LVEF response and less severe progression in terms of major cardiac events. These results, along with previous reported outcomes in TTNtv-DCM, support the idea of a genetic-based

management, with particular thresholds for therapies and devices, a less close follow-up and, last but not least, a reassuring prognostic message to these TTNtv-DCM patients.

#### Acknowledgments

We gratefully acknowledge the participation of every family member included in this research and the work of our nurses: Begoña Navarro and Natalia Maganto.

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Available online 5 February 2020

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<https://doi.org/10.1016/j.rec.2019.12.005>  
1885-5857/

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## Flow obstruction of continuous-flow ventricular assist devices. Diagnosis and treatment of an uncommon problem



### Diagnóstico y tratamiento de la obstrucción al flujo en dispositivos de asistencia ventricular de flujo continuo. Un problema infrecuente

#### To the Editor,

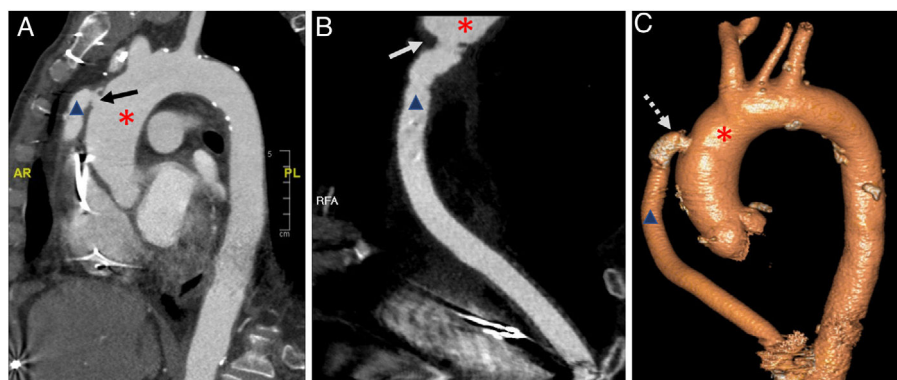
Left ventricular assist devices (LVAD) are a success story in the treatment of patients with advanced heart failure, but their use is limited by the incidence of adverse events. One of the more serious complications is device thrombosis. With third generation devices, the incidence rate for thrombosis is between 1.35 and 0.5/100 patients/mo, and thrombosis is more common within the pump. The incidence of intrapump thrombosis has been reduced by technological advances<sup>1</sup>; however, LVAD flow can also be obstructed, albeit less frequently, by torsion, thrombosis, or stenosis affecting the outflow graft (4% of thrombosis events).<sup>2</sup>

We present the case of a 72-year-old male patient with advanced heart failure in INTERMACS profile 3 who received a HeartWare HVAD System (Medtronic, United States) as destination therapy. The LVAD was implanted via left lateral thoracotomy and upper ministernotomy. The outflow graft was anastomosed in the ascending aorta. The patient was anticoagulated with sodium heparin in the first 24 hours after implantation and was

subsequently placed on oral anticoagulation therapy with acenocoumarol and antiplatelet therapy with 150 mg/d aspirin. The HeartWare HVAD parameters at discharge were as follows: speed, 2700 rpm; power, 3.6 W; and estimated flow, 3.9 L/min. Echocardiography confirmed intermittent opening of the aortic valve.

The patient's immediate clinical course was favorable. However, after the fourth month, he began to have events related to hemocompatibility. There were 2 episodes of severe anemia secondary to occult gastrointestinal bleeding that required temporary suspension of antiplatelet and anticoagulation therapies, management to achieve an INR of 2–2.5, and initiation of chronic treatment with slow-release octreotide. The patient also had a transient ischemic attack in the right middle cerebral artery.

LVAD follow-up revealed a progressive decline in estimated flow but with stable power despite blood volume optimization. This was accompanied by a decline in flow pulsatility and hemolysis data showing progressive increases in lactate dehydrogenase levels and haptoglobin metabolism, despite good INR control except during the bleeding episodes. Echocardiography revealed evidence of insufficient left ventricular emptying: aortic valve opening in all heartbeats, moderate mitral regurgitation, and displacement of the interventricular septum to the right. Thoracic computed tomography revealed stenosis of the anastomosis between the outflow graft and the ascending aorta (figure 1A,B). The outflow graft was at a 90° angle to the aorta and there was no evidence of thrombotic material, thus indicating torsion of the graft. Given the evidence



**Figure 1.** A and B, Thoracic computed tomography showing the stenosis (solid arrows) located at the level of the anastomosis of the outflow graft (triangle) with the ascending aorta (asterisk). C, Postprocedure computed tomography 3-dimensional reconstruction showing the implanted stent (dashed arrow).