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ORIGINAL RESEARCH

CIED - CRT

# Impact of DCM-Causing Genetic Background on Long-Term Response to Cardiac Resynchronization Therapy

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## ABSTRACT

**BACKGROUND** Patients with nonischemic dilated cardiomyopathy (DCM), severe left ventricular (LV) dysfunction, and complete left bundle branch block benefit from cardiac resynchronization therapy (CRT). However, a large heterogeneity of response to CRT is described. Several predictors of response to CRT have been identified, but the role of the underlying genetic background is still poorly explored.

**OBJECTIVES** In the present study, the authors sought to define differences in LV remodeling and outcome prediction after CRT when stratifying patients according to the presence or absence of DCM-causing genetic background.

**METHODS** From our center, 74 patients with DCM subjected to CRT and available genetic testing were retrospectively enrolled. Carriers of causative monogenic variants in validated DCM-causing genes, and/or with documented family history of DCM, were classified as affected by genetically determined disease (GEN+DCM) (n = 25). Alternatively, by idiopathic dilated cardiomyopathy (*id*DCM) (n = 49). The primary outcome was long-term LV remodeling and prevalence of super response to CRT (evaluated at 24-48 months after CRT); the secondary outcome was heart failure–related death/heart transplant/LV assist device.

**RESULTS** GEN+DCM and *id*DCM patients were homogeneous at baseline with the exception of QRS duration, longer in *id*DCM. The median follow-up was 55 months. Long-term LV reverse remodeling and the prevalence of super response were significantly higher in the *id*DCM group (27% in *id*DCM vs 5% in GEN+DCM; $P = 0.025$). The heart failure–related death/heart transplant/LV assist device outcome occurred more frequently in patients with GEN+DCM (53% vs 24% in *id*DCM; $P = 0.028$).

**CONCLUSIONS** Genotyping contributes to the risk stratification of patients with DCM undergoing CRT implantation in terms of LV remodeling and outcomes. (JACC Clin Electrophysiol 2024;10:1455–1464) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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**ABBREVIATIONS AND ACRONYMS**

**CRT** = cardiac resynchronization therapy

**DCM** = dilated cardiomyopathy

**EF** = ejection fraction

**HF** = heart failure

***id*DCM** = idiopathic dilated cardiomyopathy

**LBBB** = left bundle branch block

**LBBBICMP** = left bundle branch block-induced dilated cardiomyopathy

**LV** = left ventricular

**Super-Resp** = super responders

Patients with nonischemic dilated cardiomyopathy (DCM) and left bundle branch block (LBBB) represent a high-risk population with advanced heart failure (HF). Cardiac resynchronization therapy (CRT) is recommended in these patients,[1] but the response is heterogeneous. Rates of early HF deaths after implant remain high, especially considering the younger age of these patients compared with patients with ischemic cardiomyopathy and LBBB.[2] However, a minority of these patients show a complete normalization of left ventricular (LV) ejection fraction (EF) and volumes, associated with good long-term prognosis (super responders [Super-Resp]).[3,4]

The relationship between LBBB and LV function is complex and is still poorly understood[5]; LBBB more commonly appears in the natural course of DCM with severe LV dysfunction, representing a marker of disease progression associated with increased risk of all-cause mortality.[6] Alternatively, as in Super-Resp cases, the complete reversibility of LV dysfunction after resynchronization supports a role of LBBB as a direct cause of DCM, in the so-called left bundle branch block-induced dilated cardiomyopathy (LBBBICMP).[7,8]

Previous single-center studies showed that uncharacterized DCM experienced more frequently Super-Response to CRT if compared with ischemic etiology.[4] However, DCM represents an heterogeneous disease, mono-genetically determined in approximately 35% of patients.[9,10] Recent strong evidence demonstrates that specific DCM-causing genes (eg, *LMNA, DSP, FLNC, TTN*) can lead to distinct outcomes, particularly concerning the risk of progressive HF, arrhythmias, and LV remodeling.[9,11-15] The impact of DCM-causing genetic background on the response to CRT is still largely unexplored[16] and may explain in part the heterogeneity of this phenomenon.

Furthermore, in the context of genetically determined DCM, LBBB is not a common finding.[9,13,17,18] This observation suggests that the genetic background predisposing to LBBBICMP, if present, may be different from those predisposing to DCM. At the same time, if cardiomyocytes are affected by defects in genes involved in sarcomeric, cytoskeletal, nuclear, or desmosomal efficiency, the intraventricular conduction system may not be directly involved, at least in the early stages. Therefore, the presence of LBBB could represent a marker of advanced disease.

In this view, a therapeutic approach aiming to restore this electrical defect, such as CRT, may have a diminished likelihood of efficiently addressing the primary etiology of the disease. The preimplant diagnostic criteria of LBBBICMP remain currently an unmet clinical need claiming for further studies to identify earlier these patients.[9,19] Similarly, any further precise prognostic prediction after CRT should be considered clinically meaningful in patients with DCM and advanced HF.

In this single-center, retrospective study, we hypothesized that genetic test may help in stratifying patients with DCM subjected to CRT. To verify this hypothesis, we sought to describe LV remodeling and HF related outcomes after CRT according to DCM-causing genetic background.

## METHODS

**PATIENT SELECTION AND STUDY DESIGN.** We retrospectively analyzed all DCM patients with successful CRT device implantation and available genetic testing consecutively included in the CRT-Registry of our institution (an ongoing research database prospectively including all patients undergoing CRT) from January 2008 to December 2018. Follow-up ended at the date of primary outcome or in December 2021. Indications for CRT were symptomatic HF (NYHA functional class II or more) with LVEF ≤35% despite optimal medical therapy, QRS duration ≥130 ms and LBBB QRS morphology.[1] Patients with previous ICD or PM upgraded to CRT were considered not eligible. The study received Institutional Review Board approval, and informed consent was obtained under the Institutional Review Board policies of the hospital administration (CERU; N.O. 43/2009, 06/2022/Em.).

The diagnosis of DCM was performed in the presence of LVEF <50% and LV or biventricular dilatation in the absence of any known possible cause of LV dysfunction.[20] Patients were included in the Heart Muscle Registry of Trieste, that contains detailed information about family history of cardiomyopathies and SCD with a ≥3-generation pedigree. Data from 12-lead electrocardiograms and echocardiographic evaluation at baseline (preimplant or within 1 month after), and after 24 to 48 months (median 24 months), as previously described,[3] were recorded. Measurements were assessed following international guidelines.[21] CRT interrogation was periodically conducted for all the devices.

**STUDY OUTCOMES.** The primary outcome was measures of LV remodeling: 1) relative changes (Δ) in LVEF (after-CRT LVEF − before-CRT LVEF)/pre-CRT LVEF × 100) and left ventricular end-systolic volume (LVESV) (after-CRT LVESV − before-CRT LVESV)/ pre-CRT LVESV × 100) at 2 years[3,22]; or 2) Super-Resp status, defined as LVEF >50% 2 years after CRT.[3]

**TABLE 1 Main Clinical and Echocardiographic Features at Enrollment and the Procedural Details of the CRT Implantation, According to the Genetic Background**

| | Total (N = 74) | *GEN*+DCM (n = 25, 34%) | *id*DCM (n = 49, 66%) | *P* Value |
|---|---|---|---|---|
| Age at implantation, y | 58 (48-63) | 56 (46-60) | 59 (50-64) | 0.079 |
| LBBB already present at first diagnosis of DCM | 44 (60) | 4 (16) | 40 (82) | **<0.001** |
| HF duration before implant, mo | 99 (20-172) | 114 (38-158) | 91 (16-188) | 0.611 |
| LBBB at CRT implant | 74 (100) | 25 (100) | 49 (100) | 1.00 |
| LBBB, Strauss criteria | 39 (53) | 13 (52) | 26 (53) | 0.563 |
| Female | 21 (28) | 5 (20) | 16 (33) | 0.194 |
| BSA, $m^2$ | 1.95 (1.77-2.10) | 1.93 (1.78-2.14) | 1.95 (1.75-2.09) | 0.667 |
| Diabetes, % | 14 (19) | 2 (8) | 12 (24) | 0.064 |
| AF, permanent, % | 20 (27) | 10 (40) | 10 (20) | 0.088 |
| SBP, mm Hg | 110 (100-120) | 107 (100-110) | 110 (105-120) | **0.036** |
| QRS, ms | 170 (148-190) | 161 (150-171) | 175 (160-181) | **0.035** |
| LVEDV, mL | 213 (156-266) | 194 (159-259) | 215 (153-269) | 0.673 |
| LVESV, mL | 155 (106-200) | 149 (115-199) | 161 (99-206) | 0.893 |
| LVEF, % | 26 (19-31) | 25 (17-31) | 27 (19-31) | 0.398 |
| MR moderate-severe, % | 28 (38) | 10 (40) | 18 (37) | 0.489 |
| Restrictive filling pattern | 23 (31) | 9 (36) | 14 (29) | 0.346 |
| RV systolic disfunction, % | 16 (21) | 8 (32) | 8 (16) | 0.061 |
| Site of LV pacing | | | | |
| Post | 15 (20) | 5 (23) | 10 (20) | 0.117 |
| Lat | 35 (47) | 10 (40) | 25 (59) | |
| Ant-lat | 6 (8) | 4 (18) | 2 (5) | |
| Middle cardiac vein | 1 (1) | 0 | 1 (2) | |
| Post-lat | 17 (23) | 6 (27) | 11 (22) | |
| NYHA functional class | | | | |
| II | 46 (62) | 16 (64) | 30 (61) | 0.892 |
| III | 28 (38) | 9 (36) | 19 (39) | |
| ACEI/ARB, % | 66 (92) | 24 (96) | 42 (86) | 0.645 |
| Beta-blockers, % | 64 (90) | 23 (95) | 41 (84) | 0.556 |
| MRA, % | 50 (70) | 17 (68) | 33 (67) | 0.461 |
| Loop diuretic agents, % | 57 (77) | 20 (80) | 37 (75) | 0.595 |

Values are median (Q1-Q3) or n (%). **Bold** values indicates statistical significance.

ACEI = angiotensin-convertor enzyme inhibitor; AF = atrial fibrillation, ARB = angiotensin 2 receptor-blocker; BSA = body surface area; GEN = genetically determined; HF = heart failure; *id*DCM = idiopathic dilated cardiomyopathy; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricle ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; RV = right ventricle; SBP = systolic blood pressure.

The secondary outcome was a composite of cardiovascular death (DHF), heart transplant, and left ventricular assist device (VAD) implant.

**GENETIC ANALYSIS AND PATIENT'S CLASSIFICATION.** Genetic testing was performed by next-generation DNA sequencing of cardiomyopathy-related multigene panels, as previously reported.[10] DCM-validated genes (such as *TTN, LMNA, FLNC, DSP, MYH7, TNNT2, DMD,* and others) were tested among the whole cohort during the entire inclusion period. Gene variants were classified as pathogenic (P) or likely pathogenic (LP) according to the American College of Medical Genetics and Genomics criteria (ACMG).[23]

Patients found to be carrier of P/LP variants in validated gene were considered affected by monogenic DCM (*GEN*+DCM). Patients without P/LP variants, but with demonstrated family history of cardiomyopathy (documented in 1 or more relatives of 1st and/or 2nd degrees) were also considered affected by heritable, genetically determined disease and included in *GEN*+DCM population.

Patients who were not carriers of P/LP variants and with no evidence of familial disease were considered affected by sporadic, idiopathic DCM (*id*DCM).

**DEVICE IMPLANTATION.** CRT devices from major manufacturers (Biotronik, Guidant-Boston Scientific, Medtronic, Livanova-Sorin-Microport, and St. Jude Medical-Abbott) were used. The right atrial and ventricular leads were positioned conventionally. Preferred localization of the LV lead was a lateral or posterior-lateral vein. Every LV lead was implanted via coronary sinus. At the end of the procedure and during follow-up CRT pacing, parameters were optimized according to patient's status.

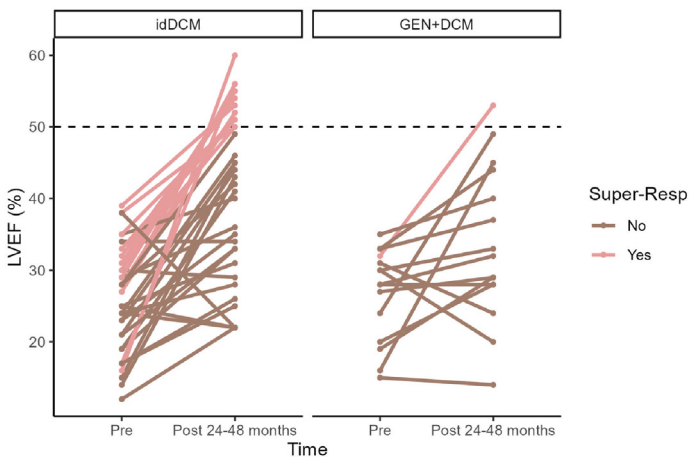
**TABLE 2 ECG, Echo, and Clinical Characteristics 2 Years After CRT Implant, According to Genetic Background**

| | Total (N = 65) | *GEN*+DCM (n = 20) | *id*DCM (n = 45) | *P* Value |
|---|---|---|---|---|
| LVEDV, mL | 137 (112-219) | 172 (134-244) | 130 (95-207) | **0.024** |
| LVESV, mL | 88 (55-158) | 101 (82-175) | 65 (51-137) | **0.032** |
| LVEF, % | 40 (28-50) | 29 (22-42) | 44 (32-52) | **0.009** |
| Restrictive filling pattern | 6 (9) | 4 (20) | 2 (4) | 0.058 |
| RV systolic disfunction | 6 (9) | 4 (20) | 2 (4) | 0.058 |
| Δ LVEDV, % | −28 (−47/−3) | −12 (−30/11) | −39 (−50/−8) | **0.038** |
| Δ LVESV, % | −42 (−64/−7) | −11 (−45/−1) | −50 (−69/−35) | **0.004** |
| QRS, ms | 140 (136-146) | 140 (122-160) | 140 (122-157) | 0.615 |
| Δ QRS, % | −17 (−25/−6) | −11 (−20/−0) | −20 (−25/−10) | **0.010** |
| BiV pacing, % | 98 (97-99) | 98 (97-99) | 98 (97-99) | 1.00 |
| Super-Resp | 13 (20) | 1 (5) | 12 (27) | **0.025** |
| NYHA functional class | | | | |
| II | 55 (85) | 15 (75) | 40 (89) | 0.055 |
| III | 10 (15) | 5 (25) | 5 (11) | |

Values are median (Q1-Q3) or n (%). **Bold** values indicates statistical significance.
BiV = biventricular; Δ = relative change; Super-Resp = super responders; other abbreviations as in Table 1.

**STATISTICAL ANALYSIS.** Summary statistics of clinical and instrumental variables were expressed as the mean ± SD, median and interquartile range (Q1, Q3), or counts and percentage, as appropriate. The longitudinal evolution of the parameters under study from basal to follow-up examination was assessed by the 2-tailed paired Student *t*-test or Wilcoxon test according to Gaussian or non-Gaussian distribution, with significance level taken as $P < 0.05$. Comparisons between groups were made by the 2-sample Student's *t*-test or the Mann-Whitney or nonparametric Mann-Whitney test; the chi-square test or the Fisher exact test was calculated for discrete variables. Linear equations associating median baseline LVEF with median LVEF at 24 to 48 months after CRT and with GEN+DCM vs *id*DCM groups were estimated using quantile regression. A model with an interaction between the 2 covariates was also considered to study whether the slope of the regression lines for the 2 groups differed. Kaplan-Meier curves were used to estimate overall survival in the population after CRT implantation and they were compared by means of the log-rank test. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed in R version 4.1.3 (R Foundation for Statistical Computing).

**FIGURE 1 Trends of LVEF Evolution From Baseline to 24 to 48 Months After CRT, in *id*DCM and *GEN*+DCM Groups**




Evolution of left ventricular ejection fraction (LVEF) after implant shows median higher improvement in idiopathic dilated cardiomyopathy (*id*DCM patients) (left) compared with genetically determined dilated cardiomyopathy (GEN+DCM) patients (right). The vast majority of super responders (Super-Resp) (pink dots) belongs to *id*DCM group."

## RESULTS

**DESCRIPTION OF STUDY POPULATION.** Among the 350 patients who underwent CRT in the selected period, 74 met the inclusion criteria of DCM with available genetic test. Of these, 25 patients (34%, *GEN*+DCM) resulted carriers of a P/LP variant in validated DCM causing genes (n = 19, 76%) or had documented family history of DCM in absence of identified P/LP variant (n = 6, 24%) (Supplemental Figure 1).

Among *GEN*+DCM carriers, the more frequent genotypes were *LMNA* (n = 6, 25% of total *id*DCM cohort) and sarcomeric genes (n = 6, 25%), followed by *TTN* (n = 4, 17%), desmosomal genes (n = 2, 8%), and *DMD* (n = 1, 4%) (Supplemental Figure 2, Supplemental Table 1).

Clinical characteristics at time of implant were similar between *GEN*+ DCM and *id*DCM patients (Table 1), especially in respect to LV geometry and function, whereas *id*DCM patients showed a relatively more prolonged QRS duration (175 ms vs 161 ms in *GEN*+DCM; $P = 0.035$). Permanent AF and RV dysfunction showed a mild, nonsignificant enrichment in *GEN*+DCM patients). As expected, LBBB was rarely present at disease's onset in *GEN*+DCM patients. Disease duration preimplant was similarly prolonged in both groups.

**LV REMODELING AFTER CRT IMPLANTATION AT 24 TO 48 MONTHS, ACCORDING TO GENETIC BACKGROUND.** In the whole population, the biventricular pacing rate was above 98% with a consistent reduction of QRS duration (mean QRS duration of 140 ±

19.4 ms), remarkably similar in the 2 groups, but with greater relative reduction in *id*DCM.

Of 74 patients enrolled, only 65 patients (86%) were evaluated for LV remodeling at 24 to 48 months (median 24 months), because 5 patients of *GEN*+DCM (20%) and 4 patients of *id*DCM group (8%) met DHF/HT/VAD outcome before this timepoint. Echocardiographic and electrocardiographic characteristics of these patients, 2 years after implant, are described in **Table 2**.

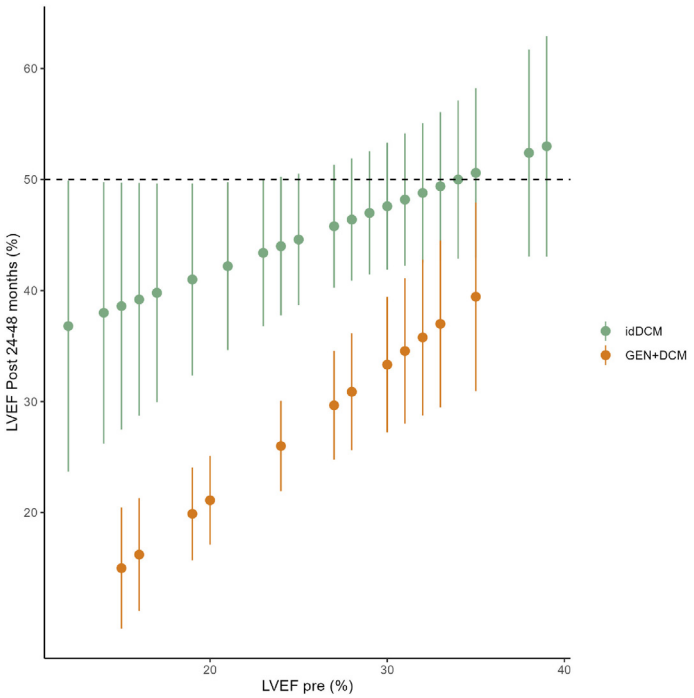
With respect to echocardiographic data at baseline, LVEF increased and LVESV reduced in both groups (**Figure 1**, Supplemental Figure 3A). However, at 2 years, patients with *id*DCM showed smaller median LV volumes and higher median LVEF with respect to patients with *GEN*+DCM, associated with a higher prevalence of Super-Resp to CRT (27% in *id*DCM vs 5% in *GEN*+DCM; $P = 0.025$) (**Table 2**). In addition, *id*DCM group was characterized by markedly higher relative improvement in LVEF (from 27% to 44% vs 25% to 29% in *GEN*+), and a greater relative reduction both in LVESV (Δ-50% vs Δ-11% in *GEN*+; $P = 0.004$) and LVEDV (Δ-39% vs Δ-12% in *GEN*+; $P = 0.038$).

Notably, a more favorable LV remodeling in *id*DCM group was confirmed at the following: 1) after the exclusion of Super-Resp from the analyses (Supplemental Figure 3B); and 2) after the exclusion of familial cases with negative genetic testing (Supplemental Table 2).

Linear associations between baseline LVEF and LVEF at 2 years after CRT were also different in the 2 groups (**Figure 2**). With respect to *GEN*+DCM, *id*DCM patients showed a median difference in the increase of LVEF after CRT of 12 points (95% CI: 7.8-22 points) after adjusting for LVEF at baseline. Furthermore, there was a nonsignificant ($P = 0.20$) trend toward different slopes of these associations, suggesting how *id*DCM patients with more severe baseline LV dysfunction may experience the greater relative improvement of LVEF.

The 20% of the study population at 2 years after CRT were Super-Resps, almost exclusively belonging to *id*DCM (92% of total Super-Resp) (**Figure 3**, **Table 2**). Of note, no significant differences were detectable at time of implant between future Super-Resp and non-Super-Resp, except for genetic background: rare in Super-Resp (1 patient of 13 Super-Resp, 8%), more frequent in other patients (37%; $P = 0.039$) (Supplemental Table 3). Furthermore, if analyzing only the *id*DCM subgroup, future Super-Resp were not clearly distinguishable from other patients (Supplemental Table 4), although Super Resp showed mildly higher values of systolic blood pressure and a trend toward less dilated LV.

**FIGURE 2 Linear Associations Between Median Preimplant LVEF and Median LVEF at 24 to 48 Months After CRT in *GEN*+DCM vs *id*DCM**

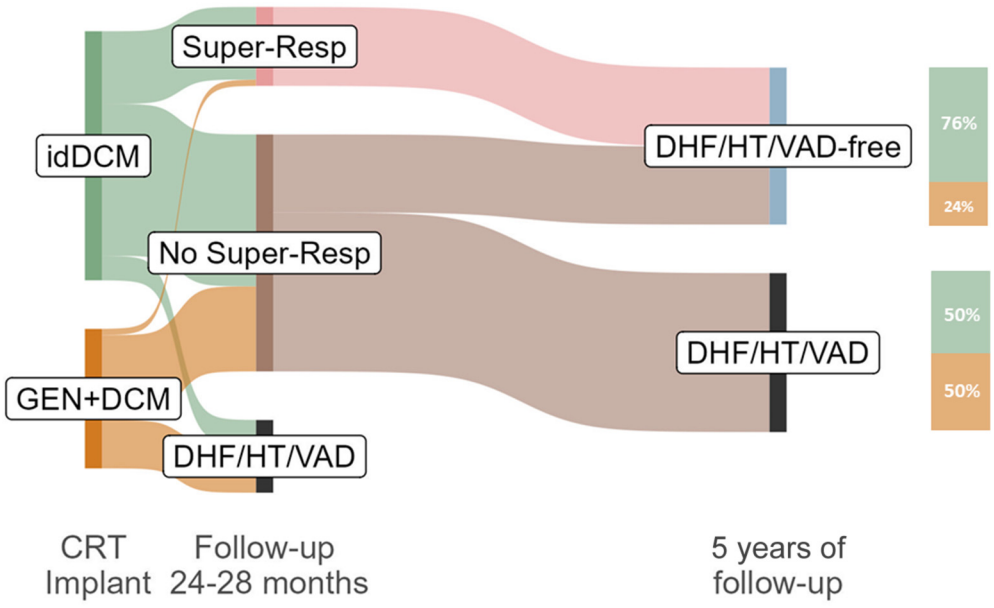



Median preimplant LVEF on x-axis and median LVEF at 24-48 Months after CRT on y-axis. For comparable preimplant LVEF values, patients with *id*DCM (light green) experience a median increase in LVEF after CRT that is 12 points higher compared with patients with *GEN*+DCM (orange). For instance: if the preimplant LVEF is 30% (x-axis), at 24 to 48 months (y-axis), the median LVEF reaches 34% for GEN+DCM, while it reaches 46% for *id*DCM patients. Abbreviations as in **Figure 1**.

**LONG-TERM OUTCOME STRATIFICATION ACCORDING TO GENETIC BACKGROUND.** **Figure 3** describes the follow-up and long-term outcomes' stratification of our cohort. The incidence of secondary outcome in the whole cohort is coherent with an advanced disease (global rate of DHF/HT/VAD of 34% at a median follow-up of 56 months [Q1, Q3: 30, 106 months]). However, patients with *GEN*+DCM experienced a significantly higher cumulative rate of these events with respect to *id*DCM (respectively 52% vs 24%) (**Table 3**, **Figure 4**).

The distribution of this outcome (n = 13, 52% of *GEN*+DCM) according to the underlying genotype was the following: of 6 *LMNA* P/LP variant carriers, 5 met this outcome over a median follow-up of 34 months (Q1, Q3: 14, 86 months). Patients with familial DCM in absence of identified monogenic variants met this outcome in 3 of 6 cases with a median follow-up of 48 months. Patients with sarcomeric P/LP variants (n = 6) showed 2 HF events (after 16 and 23 months). The remaining 3 HF events involved 2 of 4

**FIGURE 3** Sankey Diagram Associating Our Study Groups With Outcomes at 2 Years (LV Remodeling) and 5 Years (DHF/HT/VAD) After CRT Implantation




The temporal evolution of our cohorts from cardiac resynchronization therapy (CRT) implant to primary outcome (median 2 years) and secondary outcome (median 5 years). After 5 years, 75% of patients free of HF events belong to the *id*DCM group. Distribution of Super-Resp into the 2 subgroups (*id*DCM and GEN+DCM) of the study population, and association of super responder with secondary outcomes. DHF/HT/VAD: heart failure death/heart transplant/ left ventricular assist device implantation; other abbreviations as in Figure 1.

*TTN*tv carriers (after 30 and 130 months of follow-up) and 1 *DSC2* P/LP variant carrier (after 9 months of follow-up).

Notably, all Super-Resp patients (n = 13, 12 patients with *id*DCM and 1 carrying *TTN*tv) were free of HF events at long-term follow-up. A trend toward increased risk of DHF/HT/VAD for patients with *GEN*+DCM was confirmed also after the exclusion of Super-Resp from the analyses (Supplemental Figure 4).

## DISCUSSION

To the best of our knowledge, this is the first study evaluating the impact of DCM-causing genetic background in patients treated with CRT. The main findings are as follows: 1) favorable reverse LV remodeling and the prevalence of Super-Resp after CRT are significantly more common in patients with idiopathic, nonhereditary DCM; and 2) genetically determined DCM in patients subjected to CRT is associated with worse prognosis if compared with patients with *id*DCM (Central Illustration).

When considering the total amount of patients with DCM genotyped in our referral center for inherited cardiomyopathies in the study period (more than 800 patients), the relatively low number of our study population could be intended as confirmatory of the uncommon association between monogenic DCM and LBBB. However, enrolled patients were remarkably homogeneous at time of implant in respect to common clinical variables, and the subclassification according to genetic background does not allow us to enhance significant differences, with the important exception of QRS duration. The latter appears more prolonged in *id*DCM, thus expecting a potential greater benefit from CRT.

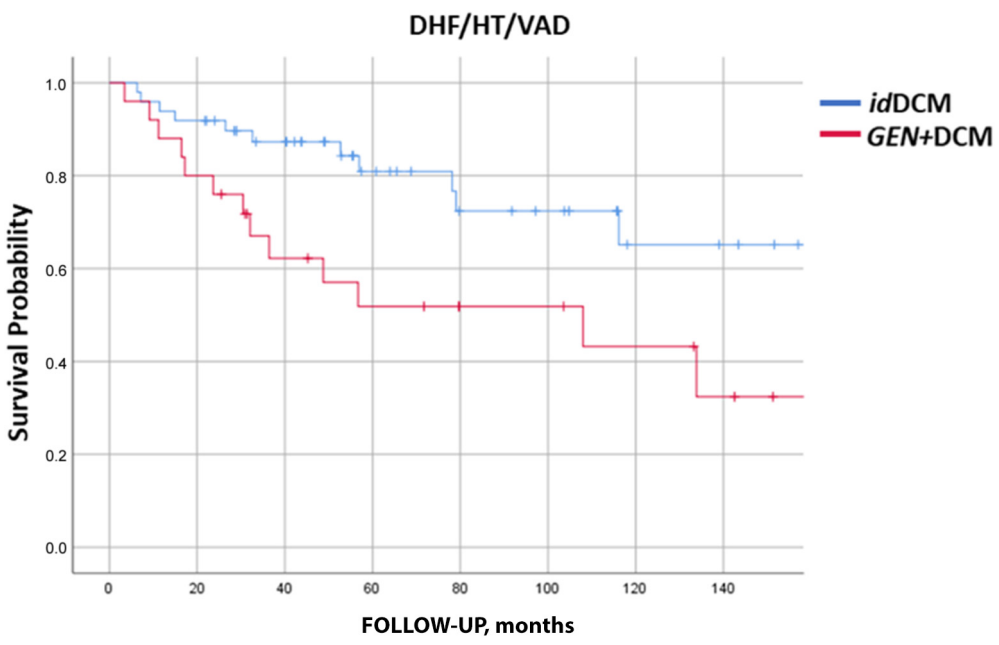
The response to CRT in *id*DCM patients showed heterogeneity in our study, in line with previous

**TABLE 3** Incidence of HFD/HT/VAD According to Genetic Background

| | Total (N = 74) | GEN+DCM (n = 25) | *id*DCM (n = 49) | *P* Value |
|---|---|---|---|---|
| DHF/HT/VAD | 25 (34) | 13 (52) | 12 (24) | **0.021** |

Values are n (%). **Bold** values indicates statistical significance.
DHF/HT/VAD = cardiovascular death, heart transplant, and left ventricular assist device.

**FIGURE 4** Survival Analysis of *GEN*+DCM Compared With *id*DCM for Secondary Outcome (DHF/HT/VAD)




Survival curves of our cohort showing *id*DCM patients (blue) associated to lower risk of HF events in respect to *GEN*+DCM (red).

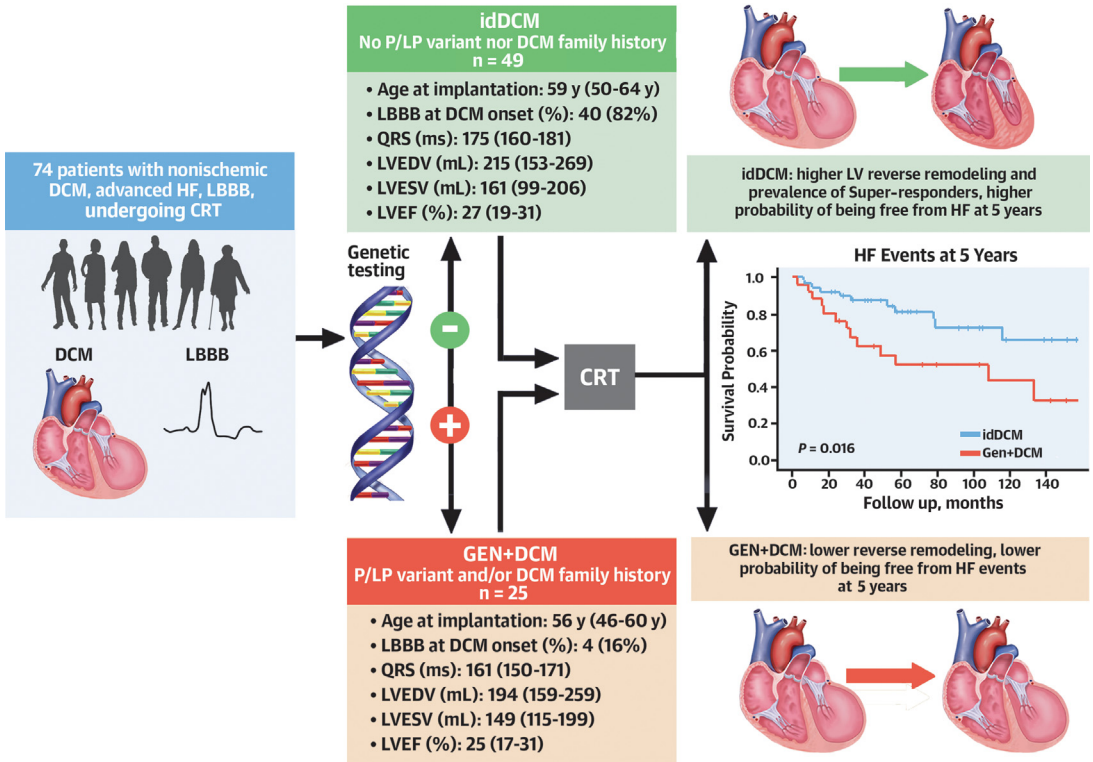
published reports about DCM: however, the vast majority of these patients develop positive reverse LV remodeling, with a substantial proportion resulting Super-Resp (27%). This significant improvement of LV function after mechanical resynchronization, associated with a good prognosis, supports a primary role of LBBB in the etiology of LV dysfunction, being more likely the cause, rather than a marker, of disease in this subgroup of patients. Even more interestingly, for the first time we demonstrated that the genetic background of Super-Resp patients does not commonly involve the actually validated DCM-causing genes. Collectively, these findings further strengthen the view of LBBBICMP as a distinct disease, both in terms of prognosis and genetic background, supporting part of the previously proposed criteria for this form of CMP.[8,19] Absence of familial history of DCM and negative genetic testing (I° and II° criteria[19]) already characterize at baseline our *id*DCM cohort. Furthermore, when focalizing the analysis inside of the *id*DCM subgroup, Super-Resp patients showed a trend toward less remodeled LV, associated with normal RV function (III° criteria). Notably, this work provides confirmation of these criteria in the largest cohort of genotyped Super Resp published nowadays.

In the same time, however, we highlight the need for a deeper characterization of the so-called "gene-elusive" DCM patients: the heterogeneity of response to CRT unravels an underlying nonhomogeneous population, which is not limited to LBBBICMP.

In our study, patients with *GEN*+DCM also present a heterogeneous response to CRT. However, with respect to LV remodeling endpoints, the trends of LVEF and LVESV at 2 years should induce the clinician to consider these patients mostly as "non-responders." In this group of patients, CRT appears in fact to more frequently stabilize and preserve baseline values of LVEF and LVESV, rather than clearly improve them. With respect to our starting hypothesis, this again is consistent with pathogenetic mechanisms involving primarily cardiomyocytes: the subsequent insurgence of cardiac conduction defect represents a further hit to cardiac mechanical function, which is intrinsically compromised.

As a consequence, *GEN*+DCM in patients was associated with a higher risk of having HF outcomes. This observation could be driven, in part, by the

**CENTRAL ILLUSTRATION** **Impact of DCM-Causing Genetic Background on Long-Term Response to CRT**




**Dal Ferro M, et al. JACC Clin Electrophysiol. 2024;10(7):1455–1464.**

Genetic testing allows more precise prognostic stratification in HF patients with newly diagnosed DCM subjected to CRT. *id*DCM is associated with higher probability of clinical, instrumental and prognostic improvement after CRT in respect to *GEN*+DCM. CRT = cardiac resynchronization therapy; DCM = dilated cardiomyopathy; EF = ejection fraction; GEN+DCM = genetically determined dilated cardiomyopathy; HF = heart failure; *id*DCM = idiopathic dilated cardiomyopathy; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; LV = left ventricular; P/LP = pathogenic/likely pathogenic; Super-Resp = super responders.

relative under-representation of Super-Resp patients within this group. However, specific survival analyses not including Super-Resp still showed a trend toward lower benefit from CRT. Notably, this post-CRT prognostic trend mirrors the prognostic trend observed in general cohorts of patients with DCM, where individuals with genetically determined disease are associated with worse outcomes than those with *id*DCM.[24] Collectively, our results provide useful prognostic information especially for newly diagnosed *GEN*+DCM with LBBB.

The paucity of patients for each distinct genotype represents a limit for genotype-phenotype correlations in this study. Furthermore, gene-specific phenotypic traits may be no more distinguishable in advanced disease, once severe LV dilation and dysfunction have occurred. Given these assumptions, in our cohort 5 of 6 patients with *LMNA*-related DCM experienced HF outcomes despite CRT, confirming the severity of *LMNA* cardiomyopathy.[9] Close monitoring of these patients seems crucial also in the early stages postimplant, especially if indications for CRT timings adhere to current guidelines.[1,16] It is already known that LBBB represents an adjunctive risk factor for adverse prognosis in *LMNA* cardiomyopathy;[16,25] this fact may prove true also in other genotypes. Defects in sarcomeric genes cause both DCM and hypertrophic cardiomyopathy, the latter rarely showing

a burnout physiology and thus resembling DCM, with worse prognosis.[26] In our cohort, patients with DCM carrying P/LP variants in sarcomeric genes may be affected by this severe form of disease. *TTNtv*-related DCM is per se associated to better prognosis and frequent reverse remodeling on optimal medical therapy with respect to other genotypes.[9,15] Partially in line with this intrinsic treatability, the unique Super-Resp patient of our *GEN*+DCM cohort was a *TTNtv* carrier, and other 2 *TTNtv* carriers showed a significant LVEF increase after CRT, whereas the fourth and last *TTNtv* carrier met the DHF/HT/VAD outcome before 2 years.

Finally, despite significant progress in understanding the genetic architecture of DCM in recent years, familial cases with demonstrated heritability and multiple negative genetic tests still are encountered in clinical practice.[10,15] Several factors may contribute to this, including technical limitation of sequencing technology and ongoing scientific advancements in the complex genetic basis of CMPs. These inconsistencies lead us to consider patients with documented family history of DCM but negative genetic test as likely affected by hereditary cardiac disease, albeit of indeterminate genetic nature.

Comprehensively, among our cohort of *GEN*+DCM, LBBB appears as an ominous sign identifying patients with advanced disease. In this scenario, the correction of LBBB by CRT seems only marginally efficient in stabilizing the clinical profile. These findings need to be validated in larger multicenter studies: if confirmed, they could lead us to reconsider optimal indications and timings for CRT in patients with *GEN*+DCM. A possible earlier insertion in transplant list could also be considered, especially if not related to *TTN* genotype.

**STUDY LIMITATIONS.** The monocentric nature of the study and the relatively small sample size of the study limit the power of our observations, requiring validation in larger cohorts. Also, because of the limited number of patients for each distinct genotype, it was not possible to perform gene-specific analyses or establish specific genotype-phenotype correlations. Furthermore, the definition of "genetically determined" DCM is nowadays usually conferred to patients carrying P/LP variants in validated DCM-causing genes, thus excluding variants classified as VUS because of insufficient evidence to properly classify them, and/or polygenic non-Mendelian genetic substrate: comprehensively, this may lead to incorrect classification of “genetically determined” DCM into the *id*DCM group. However, we believe that using heritability as a strong criterion for genetic disease may partially overcame the intrinsic limitations mentioned above.

## CONCLUSIONS

Genetic testing is useful in HF patients with newly diagnosed DCM undergoing CRT, to achieve more precise prognostic stratification. Non-hereditary, idiopathic DCM is associated with higher probability of clinical, instrumental, and prognostic improvement after CRT with respect to genetically determined DCM. The genetic background of Super-Resp patients with LBBBICMP seems not to commonly involve validated DCM-causing genes. Our data allows new insights into the relationship between LBBB and LV dysfunction.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** Genetic test results could become a pivotal element for treatment decisions in patients affected by DCM with LBBB. Negative results support CRT implantation, offering higher likelihood of clinical benefit, LV reverse remodeling, and Super-Resp status. In contrast, positive genetic results, particularly with *LMNA* variants, suggest advanced disease and a less favorable CRT response, prompting consideration of alternatives like mechanical support or HT. This patient-focused strategy, guided by genetic testing, could improve clinical decision-making, enhancing care and outcomes for DCM patients with LBBB.

**TRANSLATIONAL OUTLOOK:** The genetic background of LBBBICMP typically does not involve validated DCM-causing genes, suggesting complex, non-Mendelian etiology. Further studies are needed to dissect the causative relationship between LBBB and LV dilation and dysfunction in this form of cardiomyopathy.

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**KEY WORDS** cardiac resynchronization therapy, dilated cardiomyopathy, genetic background, LBBB, LBBBICMP, LV remodeling, super responder

**APPENDIX** For supplemental tables and figures, please see the online version of this paper.