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Heart rate reduction strategy using ivabradine in end-stage Duchenne cardiomyopathy

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ABSTRACT

Background: End-stage dilated cardiomyopathy (DCM) is the leading cause of morbidity and mortality in patients with Duchenne Muscular Dystrophy (DMD). No studies are available on the effect of ivabradine on long-term outcomes in end-stage DMD/DCM.
Methods: We prospectively enrolled a cohort of end-stage DMD/DCM patients with LV ejection fraction <40%, on chronic HF treatment with an ACE inhibitor referred consecutively from 2012 to 2017 to Bambino Gesù Children's Hospital. In each patient, before starting HRR strategy and after 1 year, we collected medical records comprehensive of clinical, demographic and imaging parameters, BNP levels, neurological and respiratory assessment.
Results: Twenty male patients with DMD/DCM with a mean age of 15.0 ± 3.5 (13–19 IQR) years were enrolled and divided into 2 groups according to ivabradine therapy. This group showed a higher incidence of MACEs compared to others in treatment with ivabradine (87.5% vs 12.5%, $p = 0.025$). At Kaplan Meier survival analysis curves, the rate free from MACEs was higher in patients treated with ivabradine (log rank $p = 0.017$). At multivariate Cox regression analysis, ivabradine therapy was an independent predictor of freedom from MACEs (H.R. 0.078, 95% CI 0.007–0.877, $p = 0.039$).
Conclusion: HRR strategy, **whether achieved by beta blockers alone or in combination with ivabradine**, seemed to be effective in reducing the incidence of acute adverse events, reaching optimal target heart rate and improving left ventricular function in DMD/DCM patients.

1. Introduction

End-stage dilated cardiomyopathy (DCM) is the leading cause of morbidity and mortality in patients with Duchenne Muscular Dystrophy (DMD) [1]. With improved respiratory support and advancement in supportive care [2–5], survival has increased to the third decade of life [5,6]. Many efforts have been made to elaborate preventive strategy for surveillance of myocardial damage and function, but in the real-world cardiac management remains still highly variable and cardiovascular drugs generally underused [7]. Over the last decade, retrospective and prospective non-randomized studies have demonstrated a benefit of β-blockers in DMD [6,8–13]. A combination therapy with ACE-inhibitors and beta-blockers had beneficial effect on long-term survival of DMD patients with left ventricular (LV) dysfunction delaying LV remodeling [9–11,13]. Indication to start β-adrenergic blockade are left to clinical judgment, and usually, treatment is started on the basis of LV dysfunction or elevated heart rate (HR). Other technologies, such as implantable defibrillator and mechanical circulatory support devices, have recently emerged as palliative treatment of end-stage DMD/DCM [14].

No established consensus is currently available in end-stage DMD/DCM and data on medical treatment are scarce.

In the adult population, ivabradine has demonstrated to reduce significantly morbidity and mortality in patients with chronic heart failure (HF) [15]. The aim of our study was to assess the impact of heart rate reduction (HRR) strategy, on long-term survival rate free from major acute cardiac events (MACEs) in end-stage DMD/DCM patients.

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2. Methods

2.1. Study design

To verify the efficacy of the HRR strategy, we prospectively enrolled a cohort of end-stage DMD-DCM patients, referred consecutively from 2012 to 2017 to Bambino Gesù Children's Hospital and Research Institute. According to previous clinical studies [7,16], we decided to include patients above 9 years old of age, in which cardiomyopathy was clinically evident.

Inclusion criteria were: 1. age at clinical presentation >9 years; 2. HR at baseline electrocardiogram (ECG) >70 bpm; 3. LV dimension >2 SD 4. LV ejection fraction <40%; 5. Chronic HF treatment with an ACE inhibitor during the study period; 6. B-type Natriuretic Peptide (BNP) value below 500 pg/mL [17].

In each patient, the clinical diagnosis of DMD was confirmed by mutational analysis from genomic DNA of the *DMD* gene or by muscle biopsy that demonstrated an absence of dystrophin by immunofluorescence or western blot (<5% dystrophin).

All patients were serially evaluated by an HF trained pediatric cardiologist in a dedicated HF Clinic, where scheduled monitoring visits and an integrative patient-centered multidisciplinary team (including neurologist, nutritionist, pneumologist, and psychologist) take care of these patients and their families.

We collected medical records comprehensive of clinical and demographic characteristics, ECG, left ventricular ejection fraction (LVEF) at echocardiography, presence of late gadolinium enhancement (LGE) by cardiac magnetic resonance imaging (CMR), BNP levels, and neurological and respiratory assessment in each patient.

To evaluate the clinical impact of the HRR strategy on MACEs incidence, we recorded all data during long-term event driven follow-up (FU).

MACEs were considered as acute HF requiring intravenous inotropes, phosphodiesterase III inhibitor or diuretics >15 days, end-stage heart failure requiring ECMO and VAD or cardiac death. Length of follow-up (FU) was calculated from the diagnosis of LVEF <40% to the date of MACEs. Informed consent was obtained from each patient's parents and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinky as reflected in a priori approval by the institution's human research committee.

2.2. Heart rate reduction strategy

We up-titrated β-blockers in all chronic end-stage DMD-DCM patients, added to a conventional therapy with ACE-inhibitors, in order to obtain an optimal HR target. HR target was defined as the reduction of HR <70 bpm, without bradycardia or symptoms related to bradycardia [15]. β-Blocker therapy (carvedilol) was initiated at 0.2 mg/kg/day and up-titrated until to 1 mg/kg/day during a total period of 2–4 months. According to the HRR protocol, all patients underwent ECG, BP measurement, echocardiogram, BNP dosage and chest x-ray. Then, patients were scheduled for follow-up visits with serial ECG and BP measurements every 2 to 4 weeks after initiation of therapy. The HRR protocol included introduction of ivabradine in addition to β-blockers to reach an HR <70 bpm [15]. After 3 months of beta-blocker titration, ivabradine was added at the initial dose of 2.5 mg twice daily increasing until 15 mg daily, whether HR was still above 70 bpm. The duration of the titration period was determined by the time needed to reach the optimal HR target. Up-titration of β-blocker and ivabradine addition was done during scheduled HF clinic visits.

This was followed by monitoring for a further 12 months on treatment, with monthly visits. HR was measured at baseline ECG before start of treatment and at every FU visit. Introduction of ivabradine was shared with the patient and his family after extended discussions regarding potential benefits (e.g., improvement of LV function), variable responses, side effects (e.g., bradycardia, phosphenes), and the absence of long-term clinical trials in this subgroup of DMD patients.

Patients who met inclusion criteria but refused the HRR protocol were considered as control group ($n = 11$ patients). In this group of patients, beta blocker therapy was up-titrated according to maximum tolerated dose and/or reduction of 20% of HR from baseline.

2.3. Cardiac imaging

All enrolled patients were serially followed-up by echocardiograms or CMR exams before the initiation of therapy and after 1 year. Inclusion echocardiographic criteria were: LV end-diastolic dimension *Z* score >2 and LV EF <40% using a Philips iE33 machine (Philips Medical Systems, Andover, MA) equipped with an X-5 or X-7 probe with M-mode, 2-dimensional (2D), Doppler. 2D images were obtained for analysis of LV volumes on 3 consecutive beats from apical 4-chamber and 2-chamber views [18]. Wall thickness and chamber dimensions were obtained from the 2D parasternal long-axis view or M-mode short-axis view at the mid-ventricular level, when perfect alignment of the left ventricle was possible, on 3 consecutive beats [18]. Images were digitally stored, and measurements were made offline in accordance with guidelines of the American Society of Echocardiography [18]. Ejection fraction was calculated using the biplane Simpson formula [18].

Cardiac magnetic resonance was performed with 1.5 T magnet (Aera, Siemens, Erlangen, Germany). Enrolled patients met the eligibility requirements, according to the guidelines of the American College [19]. Our CMR protocol was previously reported [20].

2.4. Statistical analysis

Normal distribution of parameters was assessed by the Kolmogorov-Smirnov test. Variables with normal distribution were expressed as means and standard deviations (SD), and tested for differences using a *t*-test. Non-parametric variables were expressed as median and interquartile range (IQR) and differences tested using the Mann-Whitney *U* test. Categorical variables were expressed as percentages and analysed by chi-squared test or Fisher exact test, as appropriate. Paired *t*-test or Wilcoxon rank-sum test were used for longitudinal comparison of HR, LVEF and BNP values between before HRR strategy and after 1 year. To evaluate the effect of HRR strategy protocol on HR and EF changes in ivabradine treated patients, we performed a repeated-measures ANOVA with one within-subject factor with post-hoc Bonferroni test. For this analysis, not-normally distributed continuous variables were transformed by a base 2 logarithm (Ln). For longitudinal data in the HRR group, we considered continuous values such as HR, LVEF and BNP (time at three levels: before HRR strategy, ivabradine start, and after 1 year).

Freedom-from-event survival was analysed by the Kaplan-Meier method by the log-rank test.

A multivariate Cox proportional hazards analysis was used to calculate the relative hazard ratio associated with the risk of major cardiac outcome events. Only *p* values lower than 0.05 were regarded as statistically significant. All tests were two-tailed and analyses were performed using computer software packages (SPSS-22.0, IBM, NY, USA).

3. Results

Twenty male patients with DMD/DCM with a mean age of 15.0 ± 3.5 (13–19 IQR) years were enrolled. Clinical, pharmacological and imaging characteristics are showed in Table 1. All patients used wheelchairs in their daily lives. Arm functional grade, according to CINRG Duchenne Natural History Study [7], was assessed in all patients with a median grade of 3. Fourteen (70%) patients used nocturnal non-invasive ventilatory support (NIV). Among all patients, 90% were on treatment with ß-blockers and in 45% ivabradine was added according to HRR strategy,

Table 1
Characteristics of patients with end stage DMD-DCM according to ivabradine therapy.

	HRR group ($n = 9$)	Not HRR group ($n = 11$)	*p* value
Age, years (mean, SD)	22 ± 7	19 ± 3	0.214[a]
Follow-up since diagnosis, years (median IQR)	4,5 (3−10)	3 (1–6)	0.342[b]
Age at LVEF <40%, years (mean, SD)	16 ± 3	15 ± 4	0.642[a]
NIV (%)	8 (89)	6 (55)	0.119[c]
Neurological assessment scale (median, IQR)	3 (3–4)	3 (2–3)	0.323[b]
Optimal HR target (%)	9 (100)	4 (36)	0.005[c]
HR pre-txt, bpm (mean, SD)	90 ± 12	100 ± 21	0.242[a]
HR post-txt, bpm (mean, SD)	59 ± 6	71 ± 11	0.008[a]
Systolic PA pre-txt, mm Hg (mean, SD)	100 ± 15	95 ± 15	0.467[a]
Systolic PA post-txt, mm Hg (mean, SD)	85 ± 7	90 ± 5	0.078[a]
LVEDD pre-txt, mm (mean, SD)	56 ± 4	59 ± 9	0.244[a]
LVEDD post-txt, mm (mean, SD)	47 ± 6	55 ± 9	0.023[a]
EF pre-txt, % (mean SD)	24 ± 4	30 ± 10	0.085[a]
EF post-txt, % (mean, SD)	32 ± 5	33 ± 10	0.703[a]
Ln BNP pre txt, pg/ml (mean, SD)	3 ± 1	3 ± 1	0.313[a]
Concomitant treatments			
β-Blocker dose, mg (mean, SD)	56,7 ± 28	24 ± 30	0.008[c]
ACE inhibitors [ramipril] (mg, SD)	4 ± 4	3 ± 2	0.603
Aldosterone antagonists (%)	7 (78)	6 (55)	0.272[c]
Digoxin (%)	2 (22)	3 (27)	0.604[c]
Furosemide (%)	4 (44)	8 (73)	0.205[c]
Corticosteroids (%)	6 (67)	7 (64)	0.630[c]
Aspirin (%)	5 (56)	2(18)	0.102[c]
MACEs (%)	1 (11)	7 (63)	0.025[c]

Legend = NIV: Non-Invasive Ventilation, LVEF: Left ventricular ejection fraction, IQR: Interquartile range, txt: treatment, PA: arterial pressure, LVEDD: left ventricular end diastolic diameter, EF: ejection fraction, BNP: B-natriuretic peptide, MACEs: Major adverse cardiac events, SD: standard deviations, Ln: base 2 logarithm. Optimal HR target: HR < 70 bpm, β-blocker: beta-blocker therapy.

[a] Variables with normal distribution are expressed as means and standard deviations (SD), and tested for differences using a *t*-test.

[b] Non-parametric variables were expressed as median and interquartile range (IQR) and differences tested using the Mann-Whitney *U* test.

[c] Categorical variables were expressed as percentages and analysed by chi-squared test or Fisher exact test, as appropriate.

60% furosemide, 35% aspirin, 65% eplerenone, 25% digoxin, 65% corticosteroids. According to the inclusion criteria, all patients were already treated with ACE inhibitors. Twelve (65%) children reached the optimal HR target. All patients tolerated betablocker and ivabradine therapy. At baseline, all patients presented asymptomatic arterial hypotension with no changes during therapy or dose up-titration. Only one patient had phosphenes after up-titration of ivabradine and dose was reduced with relief of this symptom. A greater percentage of HRR group patients reached an optimal HR target compared to those not in the HRR group. A higher dose of beta-blockers was used in the HRR group compared to the other group. Patients not adherent to the HRR strategy showed a significant reduction of HR from 100 ± 21 to 71 ± 11 (Fig. 1A $p = 0.004$) with a change in HR of −29 ± 16 bpm, while those in the HRR strategy group reported a significantly greater reduction of HR from 90 ± 12 bpm to 71 ± 18 bpm on β-blocker therapy and to 59 ± 6 bpm with ivabradine ($p < 0.0001$) with an overall reduction of −32 ± 11 bpm and a reduction of −12 ± 16 bpm from β-blocker to ivabradine ($p = 0.008$) (Fig. 2A). A slightly difference was noted in LVEF change in the control group, before and after β-blocker therapy of 3,4 ± 3% (Fig. 1B, $p = 0.046$), and a more significant increase in the HRR group, from 24 ± 4% before therapy to 28 ± 7% on beta-blocker therapy and to 32 ± 4% after addition of ivabradine ($p = 0.018$), with an overall increase of 8,3 ± 3,3% (Fig. 2B, $p < 0.0001$). The comparison of EF improvement in the HRR group vs EF improvement in the control group was statistically significant (8,3 ± 3,3% vs 3,4 ± 3,2%, $p = 0.003$). All patients who performed CMR showed a transmural "scar" detected by LGE, prevalently in posterolateral LV wall. No significant difference was noted in BNP changes between the two groups pre and post HRR therapy and longitudinally in each group (before and after betablocker therapy in the not HHR group and before and after ivabradine addition in the HRR group).

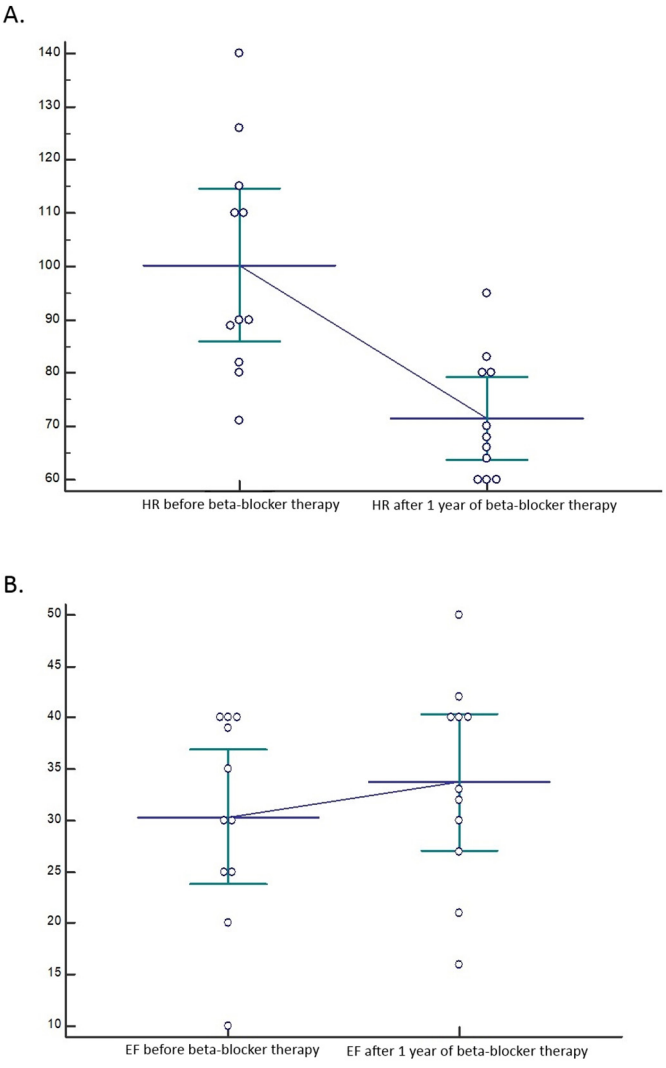

Fig. 1. Effects of Beta-blocker therapy after 1 year of treatment in the not HRR group. Panel A:HR changes before and after 1 year of beta-blocker therapy. Panel B: EF changes before and after 1 year of beta-blocker therapy. HRR = Heart Rate Reduction, HR = heart rate, EF = Ejection fraction.

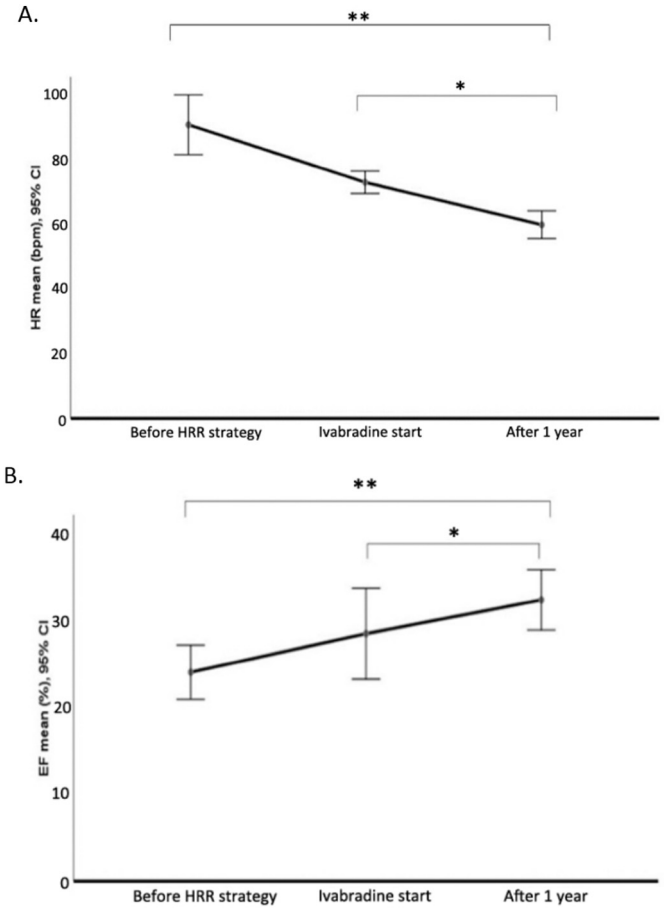

Fig. 2. Effect of HRR strategy after 1 year of treatment on HR and EF in the HRR group. Panel A: HR changes at three times: before HRR strategy, ivabradine start, after 1 year. Panel B: EF changesat three times: before HRR strategy, ivabradine start, after 1 year ** <0.0001, *<0.001, p values after Bonferroni correction. Legend: HRR= Heart Rate Reduction, HR= heart rate, EF= Ejection fraction.

Eight patients (40%) experienced MACEs. Patients not taking ivabradine had a higher incidence of MACEs compared to others in treatment with ivabradine (87.5% vs 12.5%, $p = 0.025$). At Kaplan Meier survival analysis curves, the survival rate free from MACEs was higher in patients treated with ivabradine compared to those not-treated (log rank $p = 0.017$) (Fig. 3). At multivariate analysis, ivabradine therapy was an independent predictor of freedom from MACEs (H.R. 0.118, 95% CI 0.014–0.969, $p = 0.047$).

4. Discussion

Our study evaluates for the first time the effect of an HRR strategy, using ivabradine, on MACEs in end-stage DMD-DCM. All our DMD patients had a severe clinical stage, defined according to the CINRG Duchenne Natural History Study [7] concomitantly with a severe LV dysfunction. The HRR strategy demonstrated to be effective in reducing cardiac events in end-stage DMD-DCM when compared to group not adherent to this medical management. Lowering heart rate has been

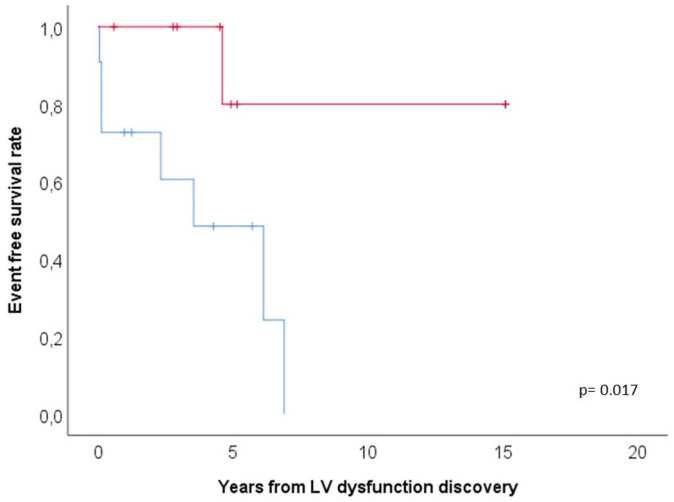

Fig. 3. Event free survival Kaplan Meier curve for MACEs in all end-stage DMD-DCM patients divided in the HRR group (red) and not HRR group (blue). Legend: MACEs = Major Adverse CardiacEvents, HRR = Heart Rate Reduction.

demonstrated to improve survival in adult population with chronic HF [21]. Similar benefit has not been fully investigated in pediatric age and the use of beta adrenergic blockade still remains controversial [8–13]. Recently, in a multicenter, randomized, placebo controlled trial in children with symptomatic HF due to DCM, ivabradine was effective in reducing HR and showed a favourable trend on clinical status and quality of life [22]. However, in this trial DMD were excluded and the follow up was restricted to 6 months [22]. Only an adult patient affected by DMD was treated with ivabradine with beneficial effect on HR and LVEF [23]. In DMD population, HR reduction with beta-blockers has been used to prevent LV dysfunction [6,8,10–13,24]. Our study showed that a significant reduction of HR was obtained by the introduction of ivabradine in end stage DMD-DCM. Interestingly, in the HRR group, a higher HR reduction was associated to an improvement of LV function after the first year of follow up. These data are consistent with BEAUTIFUL Echo sub-study, which reported a decrease of LVESV and an LVEF improvement in chronic CAD with LV systolic dysfunction [25]. In DMD population, LV dysfunction has been related to the total extent of LGE [26]. Advanced cardiomyopathy showed occurrence of mixed (intramural septal in addition to subepicardial LV lateral wall) LGE as well as presence of a (regional) transmural pattern of LGE as an independent predictor for adverse cardiac events [26]. In our cohort of end-stage DMD patients, LV scar, detected by CMR, was transmural in all patients. In DMD patients, transmural pattern has been demonstrated to correlate with the severity degree of LV systolic dysfunction, and to be an independent predictor of cardiac events [26], so in our end-stage DMD population, we could not analyse its impact on MACEs. Different mechanisms have been postulated to explore ivabradine effect on left ventricular improvement. Experimental studies showed that ivabradine is able to reduce fibrosis inhibiting the accumulation of collagen [27]. Ivabradine also constrains p38 MPK inflammatory pathways and regulates calcium metabolism, allowing the delay of LV deterioration in end stage of the disease [28].

Others drugs have been used to retard LV dysfunction in DMD patients by inhibiting progression of scar. Efficacy of eplerenone, added to ACE or ARB therapy, has been recently showed in a randomized multicenter double-blind placebo-controlled trial in a cohort of DMD patients with preserved EF [29] by reducing myocardial fibrosis progression assessed by CMR. Conflicting results have been reported about corticosteroid effect [13,30–32]. In our study, no differences in eplerenone treatment neither in corticosteroid use were found between the two groups of end-stage DMD. No longitudinal changes were observed in BNP levels, which remained stable and in the normal range, independently from HRR therapy. Our data are in agreement with previous reports in DMD, that demonstrated no BNP changes before and after beta-blocker therapy [9,12]; to our knowledge, no data are available on BNP variations after ivabradine addition in end-stage DMD-DCM.

For the first time, we observed a significant reduction of incidence of MACEs in end stage DMD-DCM patients treated **with HRR strategy**. Previously, in the SHIFT trial a significant decrease of cardiovascular death and heart failure hospitalization for worsening HF has been demonstrated by introduction of ivabradine [15]. We cannot exclude that the effect of ivabradine on MACEs incidence might be due to the lowering of heart rate, but the small number of MACEs couldn't allow a statistical evaluation of the influence of this variable. However, only with larger prospective studies we could explore this issue. Our data suggest that a robust heart rate reduction can be useful to reduce MACE incidence in a long term FU. This strategy could be safely used in patients with severe end stage DMD/DCM with an increased risk to develop an acute event, even lethal.

4.1. Limitations

This is a not-randomized single center study, subject to inherent limitations. This study was not powered to demonstrate ivabradine effects on mortality. Although the improvements on heart rate and left ventricular function were beneficial, and effects on MACEs seem to be promising, additional studies with larger sample size are needed to confirm and define the role played by ivabradine in the clinical management of end-stage DCM in DMD patients. Basing on discretional adherence to the protocol, we interpreted these data only as a pilot study, potentially useful to design future studies on HRR strategy on mortality in end-stage DMD patients. Finally, the control group was constituted from end-stage DMD patients refusing HRR protocol.

5. Conclusions

Aggressive HRR strategy in end-stage DMD/DCM population is beneficial, whether achieved by β-blockers alone or in combination with ivabradine. This strategy seemed to be effective in reducing the incidence of acute adverse events during long-term follow-up, in reaching optimal target heart rate and improving LV function in end-stage DMD/DCM patients. Then, the use of ivabradine, added to conventional heart failure therapy in these patients, may be beneficial and has a good safety profile, but deserves further investigations with larger prospective clinical trials.

Declaration of interest

None.

Financial disclosure

None.

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Clinical perspectives competencies in medical knowledge and translational outlook

- End-stage dilated cardiomyopathy (DCM) is the leading cause of morbidity and mortality in patients with Duchenne Muscular Dystrophy (DMD), but medical therapy is generally underused in end stage DMD-DCM.

- Heart rate reduction (HRR) strategy **whether achieved by β-blockers alone or in combination with ivabradine** proved to obtain the optimal target heart rate (<70 bpm) and to improve LV function in end-stage DMD-DCM patients.
- HRR strategy demonstrated to reduce the incidence of acute adverse events during a long term follow up.
- Ivabradine expands consideration for treatment of end-stage DMD-DCM patients.

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