JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 70, NO. 10, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2017.07.725

Ivabradine in Children With Dilated Cardiomyopathy and Symptomatic Chronic Heart Failure

Damien Bonnet, MD, PhD,[a] Felix Berger, MD,[b] Eero Jokinen, MD,[c] Paul F. Kantor, MD,[d] Piers E.F. Daubeney, DM[e]

ABSTRACT

BACKGROUND Heart rate reduction as a therapeutic target has been investigated in adults with heart failure (HF). Ivabradine has shown promising efficacy, but has not been evaluated in children. Currently, treatment recommendations for chronic pediatric HF are based mainly on chronic HF guidelines for adults.

OBJECTIVES The authors explored the dose-response relationship of ivabradine in children with dilated cardiomyopathy and symptomatic chronic HF. The primary endpoint was ≥20% reduction in heart rate from baseline without inducing bradycardia or symptoms.

METHODS This was a randomized, double-blind, placebo-controlled, phase II/III study with 12 months of follow-up. Children (n = 116) receiving stable HF therapy were randomized to either ivabradine or placebo. After an initial titration period, the dose was adjusted to attain the primary endpoint. Left ventricular function (echocardiography), clinical status (New York Heart Association functional class or Ross class), N-terminal pro–B-type natriuretic peptide, and quality of life (QOL) were assessed.

RESULTS The primary endpoint was reached by 51 of 73 children taking ivabradine (70%) versus 5 of 41 taking placebo (12%) at varying doses (odds ratio: 17.24; $p < 0.0001$). Between baseline and 12 months, there was a greater increase in left ventricular ejection fraction in patients taking ivabradine than placebo (13.5% vs. 6.9%; $p = 0.024$). New York Heart Association functional class or Ross class improved more with ivabradine at 12 months than placebo (38% vs. 25%; $p = 0.24$). There was a trend toward improvement in QOL for ivabradine versus placebo ($p = 0.053$). N-terminal pro–B-type natriuretic peptide levels decreased similarly in both groups. Adverse events were reported at similar frequencies for ivabradine and placebo.

CONCLUSIONS Ivabradine safely reduced the resting heart rate of children with chronic HF and dilated cardiomyopathy. Ivabradine's effect on heart rate was variable, highlighting the importance of dose titration. Ivabradine treatment improved left ventricular ejection fraction, and clinical status and QOL showed favorable trends. (Determination of the efficacious and safe dose of ivabradine in paediatric patients with dilated cardiomyopathy and symptomatic chronic heart failure from ages 6 months to 18 years; ISRCTN60567801)
(J Am Coll Cardiol 2017;70:1262–72) © 2017 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]M3C-Necker, Hôpital Necker Enfants Malades, AP-HP, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; [b]Department of Congenital Heart Disease and Pediatric Cardiology, Deutsches Herzzentrum Berlin and Charité-Universitätsmedizin Berlin, Berlin, Germany; [c]Department of Pediatrics, Division of Pediatric C, Helsinki University Children's Hospital, Helsinki, Finland; [d]University of Alberta, Stollery Children's Hospital, Edmonton, Alberta, Canada; and the [e]Royal Brompton Hospital and Imperial College, London, United Kingdom. This study has been funded by Servier. All authors (or their institutions) have received honoraria from Servier for serving as members of the scientific advisory board for this study. Dr. Bonnet has received fees for consulting activities from Novartis and Bayer Health Care. Dr. Berger has received honoraria for lectures or advisory board activities from, has participated in clinical trials for, and/or has received research funding from the following companies: Actelion, Edwards, Gore Medical, Medtronic, Novartis, Pfizer Pharma, Philips, Servier, and St. Jude. Dr. Kantor has served as a consultant for Servier and Novartis. Dr. Daubeney has received support (modest) from the Biomedical Research Unit at the Royal Brompton Hospital; and has served as a director and shareholder of DMNoMore Limited. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 18, 2016; revised manuscript received July 5, 2017, accepted July 10, 2017.

An important cause of mortality and morbidity in children, pediatric heart failure (HF) contributes substantially to health care costs (1). Pediatric cardiomyopathies are a prominent cause of HF in children, with an annual incidence of 11 to 12 children per million/year in the United States and Australia (2,3). Dilated cardiomyopathy (DCM) represents one-half of all cardiomyopathies in children. Although the overall incidence of pediatric DCM is low, it is higher in children age <1 year (44 cases per million/year) than in children older than age 3 years (3.4 cases per million/year) (4). Although some children recover normal left ventricular (LV) function and size (5), DCM is often associated with poor outcomes. Approximately 40% of children undergo cardiac transplantation or die within 5 years of DCM diagnosis, attesting to the importance of HF in this patient population (6,7).

SEE PAGE 1273

Management of children with chronic HF can be challenging. Proposed treatment guidelines for HF in childhood have been hampered by a paucity of evidence-based pediatric data (8,9). Available therapies include angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, diuretic agents, and digoxin (10,11). However, with a lack of clinical trials, these treatments are not approved for use in children. Nonetheless, these agents have been shown to be beneficial in small studies as well as in current practice, and as such, they are proposed in the guidelines for the management of chronic HF in children (8,9). To date, no randomized controlled trial of any medication has demonstrated a significant improvement of HF outcomes in pediatric patients. A study in 161 children ages 0 to 17 years with chronic HF (12) indicated that the beta-blocker carvedilol had no significant effect on chronic HF outcomes in children compared with placebo, although there was some improvement in left ventricular ejection fraction (LVEF).

In adults, an elevated heart rate is associated with an increased risk of death in patients with chronic HF (13–15). Ivabradine, an effective heart rate–reducing agent, lowers incidence of cardiovascular death and hospitalization for worsening HF in adult patients, with a relative risk reduction of 18% in a trial setting ($p < 0.0001$) (16). Ivabradine is recommended for the treatment of chronic HF in adults with an elevated heart rate and in sinus rhythm (17). There are no corresponding data for ivabradine in children. The objective of our study was to document the effect of ivabradine therapy in a pediatric population age 6 months to 18 years with DCM and symptomatic chronic HF. We explored the dose of ivabradine that was necessary to reach a ≥20% reduction in heart rate, and we evaluated its tolerance. We also describe its effect on clinical symptoms, LV function, quality of life (QOL), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) values.

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

DCM = dilated cardiomyopathy

HF = heart failure

LV = left ventricle/ventricular

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

NT-proBNP = N-terminal pro-B-type natriuretic peptide

QOL = quality of life

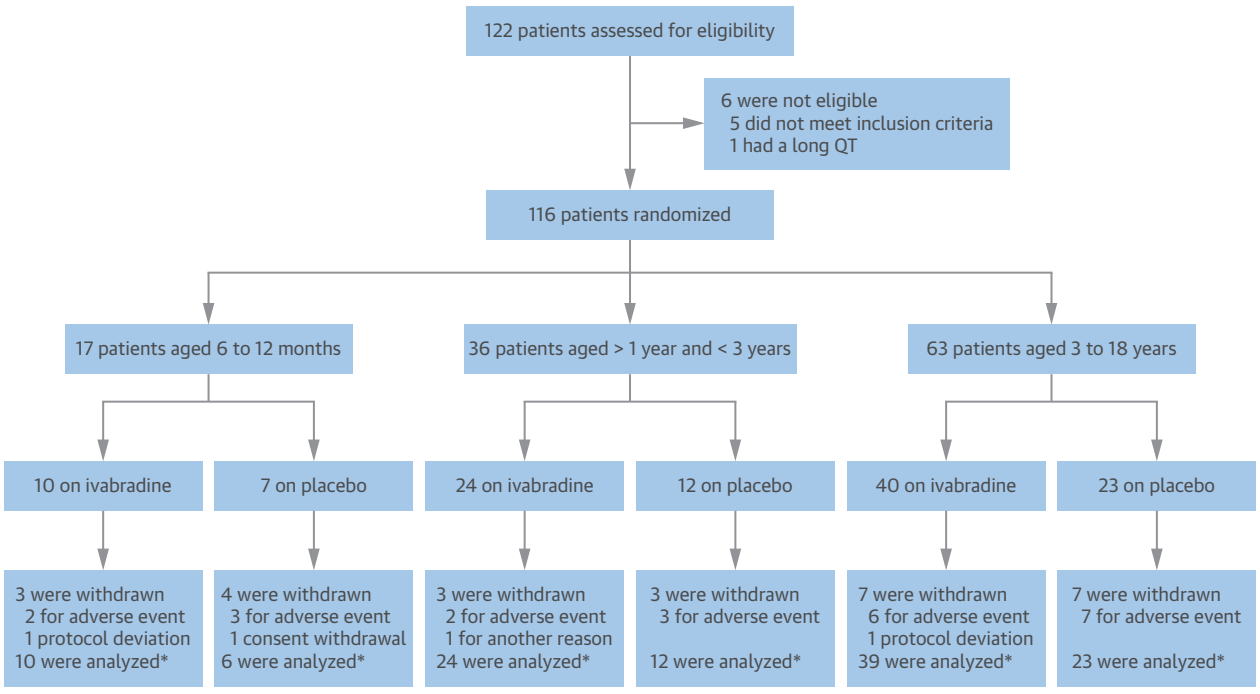
METHODS

STUDY DESIGN AND PATIENTS. This was a randomized, double-blind, placebo-controlled, phase II/III study in 47 centers across 16 countries. Children diagnosed with DCM with a history of class II to IV symptomatic HF (New York Heart Association [NYHA] functional class or Ross classification [18]), and an LVEF ≤45% (documented by echocardiography) on stable treatment for chronic HF were considered eligible. Patients enrolled were stratified into 3 subgroups (age 6 to 12 months, >1 year and < 3 years, and 3 to 18 years), and were then randomly allocated to treatment with either ivabradine or placebo in a 2:1 ratio. Treatment was allocated via a centralized interactive randomization response system. The primary objectives of the study were to: 1) determine the optimal dose of ivabradine to reach a target heart rate reduction of ≥20% without bradycardia; and 2) assess the pharmacokinetic profile and pharmacokinetic-pharmacodynamic relationship of ivabradine in children. This report describes the results pertaining to the target heart rate reduction. Pharmacokinetic results have been reported in separate publications (19,20).

Study inclusion required HF functional class to be stable for at least 4 weeks prior to selection. Eligible patients were in sinus rhythm with resting heart rates in the normal range for age: ≥105 beats/min for patients ages 6 to 12 months, ≥95 beats/min for >1 year and <3 years, ≥75 beats/min for 3 to 5 years, and ≥70 beats/min for 5 to 18 years; these values were predefined according to normal limits reported in healthy pediatric patients (21). Lower-limit values were pre-specified, because most patients were already receiving beta-blockers. The minimal resting heart rate at inclusion for 5- to 18-year-olds was fixed at ≥70 beats/min based on studies in adults (16). Neonates and infants (age <6 months) were excluded due to concerns over tolerability of the use of 2 heart rate–lowering agents (beta-blockers and ivabradine) (22,23).

The protocol was approved by the ethics committee or institutional review board at each center and conformed to the principles outlined in the Declaration of Helsinki. The parents or guardians of all

FIGURE 1 Study Flow



A total of 116 patients were subdivided by age group and randomized to ivabradine or placebo in a 2:1 ratio. *Patients included in the full analysis set (i.e., randomized patients having received at least 1 dose of treatment and with at least 2 evaluations of heart rate).

patients gave their written informed consent, and depending upon age and local regulations, children and adolescents also gave their informed assent. The International Scientific Board had the overall scientific responsibility of the study, and the Data and Safety Monitoring Board operated independently of the study's sponsor and reviewed safety data. The trial is registered on the European Clinical Trials Register (ISRCTN60567801).

PROCEDURES AND ENDPOINTS. There was a 2- to 8-week titration period with periodic visits. Previous results in adults showed that the greatest heart rate reduction with ivabradine (19% to 25%) was obtained in patients with the highest heart rate at baseline, which correlated with the greatest improvement in outcome events versus placebo (24). A mean heart rate reduction of 20% was observed to be clinically beneficial for adult patients in the SHIFT (Ivabradine and Outcomes in Chronic Heart Failure) study (16). Consequently, the dosage of study treatment was uptitrated to achieve a ≥20% reduction in heart rate without inducing bradycardia or its symptoms. Bradycardia was defined as a heart rate of <80 beats/min for patients ages 6 to 12 months, <70 beats/min for >1 year and <3 years, and <50 beats/min for 3 to 18 years. If the patient experienced bradycardia, the study drug was down-titrated to the next lowest dosage.

Study treatment was administered as an oral liquid at a starting dose of 0.02 mg/kg twice daily for children ages 6 to 12 months and 0.05 mg/kg twice daily for children ages >1 year and < 3 years or 3 to 18 years. This liquid ivabradine was specially formulated for this pediatric study, and was delivered as single-dose units of 10 ml containing 1, 5, or 13.3 mg of ivabradine (stored at room temperature). The tablet form (adult formulation) was administered to children weighing ≥40 kg with a starting dose of 2.5 mg twice daily. The doses could be adjusted every 2 weeks (increased, decreased, or maintained). The duration of the titration period was governed by the magnitude of heart rate reduction and could last up to 8 weeks or until the patient reached the primary endpoint (≥20% reduction in heart rate without bradycardia or symptoms of bradycardia).

Titration could involve a maximum of 4 steps. Patients who were initiated on 0.02 mg/kg twice daily could be uptitrated to 0.05, 0.10, 0.15, and 0.20 mg/kg twice daily, and those initiated on 0.05 mg/kg twice daily could be uptitrated to 0.10, 0.15, 0.20, and

0.30 mg/kg twice daily. Patients weighing ≥40 kg, who started on 2.5 mg twice daily (tablet form), could be uptitrated to 5, 7.5, 10, and 15 mg twice daily.

The titration period was followed by a 2-week maintenance period. This was followed by monitoring for a further 12 months on treatment, with monthly visits up to 3 months, and then visits at 6, 9, and 12 months.

At every visit, patient heart rate was measured using any method, provided that the child was quiet and at rest, and the dose of study treatment was recorded. The mean dose was calculated in the per-protocol population by averaging the daily dose received during the titration period. Electrocardiograms were reviewed centrally (CardiaBase, Nancy, France) for intervals and abnormalities. Changes in LVEF (biplane Simpson method) and other echocardiographic parameters, clinical symptoms (NYHA functional class or Ross classification), and NT-proBNP were monitored as secondary endpoints. Health-related QOL was evaluated in an optional substudy in a selection of countries and was assessed in children between 2 and 18 years of age using the Pediatric Quality of Life inventory (PedQL) 4.0 (25). Parents of children ages 2 to 5 years responded to the questionnaire themselves. Children ages 5 to 18 years personally responded to age-adapted questionnaires, as did their parents. The improvement in total score (0 to 100 scale) was expressed as a change from baseline of >4.5.

The safety of ivabradine was monitored throughout the study. Moreover, patients were hospitalized overnight for medical observation after the first treatment administration, and observed for at least 4 h after the second intake. All treatment-emergent adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities (26).

STATISTICAL METHODS. The sample size was determined based on the pharmacokinetic objective, which was 1 of the study's primary objectives. Considering the unbalanced design between ivabradine and placebo (2:1), it was estimated that at least 90 evaluable children were to be included in this study (60 ivabradine, 30 placebo) to explore the pharmacokinetic-pharmacodynamic relationship of ivabradine. This number of patients allowed the detection of a difference of at least 10% in LVEF units between ivabradine and placebo, assuming an SD of 12%, with a 95% power and a type I error of 5% (2-sided), based on a Student *t* test.

The baseline characteristics are presented as means ± SD for continuous variables and as numbers

TABLE 1 Baseline Demographics

	Ivabradine (n = 74)	Placebo (n = 42)	All (N = 116)
Demographic characteristics			
Age, yrs			
Mean ± SD	5.8 ± 5.1	5.8 ± 4.6	5.8 ± 4.9
Median (range)	3.4 (0.5–17.2)	5.3 (0.6–15.8)	3.9 (0.5–17.2)
6–12 months			
Mean ± SD	0.7 ± 0.2	0.7 ± 0.1	0.7 ± 0.2
Median (range)	0.8 (0.5–1.0)	0.7 (0.6–1.0)	0.7 (0.5–1.0)
n	10	7	17
>1 yr and < 3 yrs			
Mean ± SD	2.2 ± 0.6	2.1 ± 0.6	2.1 ± 0.6
Median (range)	2.2 (1.0–3.0)	2.3 (1.1–2.8)	2.3 (1.0–3.0)
n	24	12	36
3–18 yrs			
Mean ± SD	9.3 ± 4.6	9.3 ± 3.4	9.3 ± 4.2
Median (range)	8.9 (3.0–17.2)	8.6 (4.2–15.8)	8.6 (3.0–17.2)
n	40	23	63
Male	39 (53)	25 (60)	64 (55)
Caucasian	66 (89)	36 (86)	102 (88)
Heart rate, beats/min			
Mean ± SD	102 ± 21	100 ± 19	101 ± 20
Median (range)	101 (70–165)	96 (73–136)	100 (70–165)
Disease characteristics			
Time since diagnosis, months			
Mean ± SD	47.6 ± 51.2	48.7 ± 47.7	48.0 ± 49.7
Median (range)	27.5 (1–200)	24.0 (1–169)	25.5 (1–200)
NHYA or Ross functional class			
II	59 (80)	34 (81)	93 (80)
III	12 (16)	6 (14)	18 (16)
IV	3 (4)	2 (5)	5 (4)
LVEF, %			
Mean ± SD	32 ± 8	35 ± 8	33 ± 8
Median (range)	32 (13–45)	37 (18–44)	34 (13–45)
NT-proBNP, pg/ml			
Geometric mean	478	495	484
Median (range)	376 (17–13,255)	393 (19–2,0227)	380 (17–20,227)
n	71	41	112
Dilated cardiomyopathy cause			
Idiopathic	45 (61)	20 (48)	65 (56)
Post-viral myocarditis	16 (22)	9 (21)	25 (22)
LV noncompaction	11 (15)	11 (26)	22 (19)
Ischemic	0	2 (5)	2 (2)
Post-anthracycline	2 (3)	0	2 (2)
Concomitant treatment			
ACE inhibitors	70 (95)	39 (93)	109 (94)
Diuretic agents			
Aldosterone antagonists	63 (85)	28 (67)	91 (79)
Other diuretic agents	49 (66)	31 (74)	80 (69)
Beta-blocking agents	59 (80)	29 (69)	88 (76)
Digitalis	39 (53)	19 (45)	58 (50)
Angiotensin II antagonists	2 (3)	2 (5)	4 (4)

Values are n (%) unless otherwise indicated.

ACE = angiotensin-converting enzyme; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association.

TABLE 2 Primary Endpoint and Additional Parameter Changes in Full Analysis Set

Primary Endpoint at End of Titration	Ivabradine (n = 73)	Placebo (n = 41)	Odds Ratio (95% CI)	p Value*
All children	51/73 (70)	5/41 (12)	17.24 (5.91 to 50.30)	<0.0001
6–12 months	6/10 (60)	1/6 (17)	7.50 (0.62 to 90.63)	0.113
1–3 yrs	17/24 (71)	0/12 (0)	NA†	
3–18 yrs	28/39 (72)	4/23 (17)	12.09 (3.35 to 43.66)	0.0001
Change in Heart Rate From Baseline (beats/min)			**Mean Difference (95% CI)**	
To end of titration				
All children	−21.2 ± 13.3	−1.4 ± 11.5	−18.99 (−23.75 to −14.23)	<0.0001
6–12 months	−25.0 ± 12.4	−4.2 ± 16.5	−17.12 (−29.57 to −4.68)	0.0108
>1 yr and <3 yrs	−26.4 ± 11.2	1.3 ± 10.5	−27.54 (−35.59 to −19.50)	<0.0001
3–18 yrs	−17.1 ± 13.6	−2.1 ± 10.9	−14.56 (−21.20 to −7.92)	<0.0001
To 12 months				
All children	−20.8 ± 15.9	−3.0 ± 11.6	−16.63 (−21.91 to −11.34)	<0.0001
Change in LVEF from Baseline, %				
To 6 months				
All children	11.4 ± 11.6 (n = 72)	5.3 ± 10.3 (n = 39)	5.11 (0.87 to 9.35)	0.0186
To 12 months				
All children	13.5 ± 13.1 (n = 72)	6.9 ± 11.4 (n = 39)	5.57 (0.75 to 10.40)	0.024
Change in Total PedQL‡ Score From Baseline				
To 6 months				
All children	9.1 ± 17.3 (n = 36)	−1.5 ± 13.6 (n = 19)	9.64 (1.83 to 17.46)	0.0166
To 12 months				
All children	9.1 ± 14.2 (n = 36)	1.3 ± 15.3 (n = 19)	6.92 (−0.08 to 13.93)	0.0527
Patients With Change in PedQL‡ Score >4.5 From Baseline				
To 6 months				
All children	20/34 (59) (n = 36)	9/19 (47) (n = 19)		0.566
To 12 months				
All children	20/33 (61) (n = 36)	10/19 (53) (n = 19)		0.771

Values are n/N (%) or mean ± SD unless otherwise indicated. *p value of test for heterogeneity of odds ratio (treatment × age class) is 0.95 (NS). †Not applicable; odds ratio could not be calculated because no patient in placebo group reached the primary endpoint. ‡PedQL assessed by parents.

CI = confidence interval; PedQL = Pediatric Quality of Life inventory; other abbreviations as in Table 1.

and percentages for categorical variables. At the end of the titration period, the number and percentage of patients who reached the primary endpoint (achievement of target heart rate reduction) are presented for patients in the full-analysis set (FAS) population (i.e., all patients having received at least 1 dose of treatment and at least 2 evaluations of heart rate: at baseline and at least 1 time during follow-up). These data were also recorded for patients in the per-protocol population (i.e., all patients having completed the titration period in accordance with the protocol).

For the primary endpoint, treatment effect was estimated using a logistic regression model adjusted for age group in the overall population, and unadjusted in each age class. An estimate of the odds ratio (OR) between treatment groups and corresponding 95% confidence interval (CI) and p value are provided.

Changes from baseline to the end of titration period and 12 months (for heart rate), and to 6 and 12 months (for echocardiographic parameters and PedQL [total score]) are presented in the FAS population using a covariance analysis adjusted for age group and with baseline as a covariate. For these analyses, missing data were imputed using the last observation carried forward approach. Estimates of the mean difference between treatment groups (as E ± SE), and corresponding CI and p values are provided.

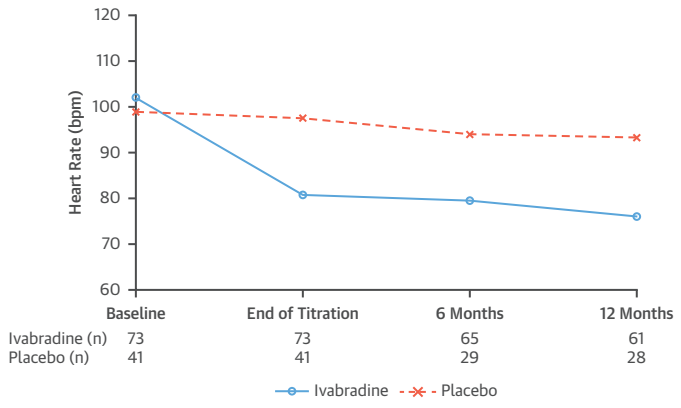
For analysis of NYHA functional class or Ross class, we performed descriptive statistics on the changes from baseline at 6 and 12 months, expressed in terms of improvement, stability, or worsening in HF class. A chi-square test was used to compare the percentage of patients who had an improvement in NYHA functional class or Ross class between treatment groups.

TABLE 3 Ivabradine Dosing: Per-Protocol Population* of Children Who Reached the Primary Endpoint

Age 6–12 months	
Mean dose during titration period, mg/kg	0.09 ± 0.04 (0.11)
Dose at the end of titration period, mg/kg	
0.02	1/4 (25)
0.05	–
0.10	–
0.15	1/4 (25)
0.20	2/4 (50)
Age >1 yr and <3 yrs	
Mean dose during titration period, mg/kg	0.13 ± 0.04 (0.15)
Dose at the end of titration period, mg/kg	
0.05	1/14 (7)
0.10	3/14 (21)
0.15	1/14 (7)
0.20	1/14 (7)
0.30	8/14 (57)
Age 3–18 yrs, <40 kg	
Mean dose during titration period, mg/kg	0.10 ± 0.04 (0.11)
Dose at the end of titration period, mg/kg	
0.05	4/17 (24)
0.10	3/17 (18)
0.15	3/17 (18)
0.20	5/17 (29)
0.30	2/17 (12)
Age 3–18 yrs, >40 kg	
Mean dose during titration period, mg/kg	4.06 ± 2.16 (3.27)
Dose at the end of titration period, mg/kg	
2.5	4/11 (36)
5.0	5/11 (46)
7.5	–
10	–
15	2/11 (18)

Values are mean ± SD (median) or n/N (%). *The mean dose was defined as the sum of doses prescribed, taking into account the number of days for which a dose was prescribed during the titration period. Dosing was twice daily.

FIGURE 2 Heart Rate at Rest



Mean resting heart rate began decreasing with ivabradine almost immediately upon administration.

For the analysis of NT-proBNP, we performed descriptive statistics on the changes from baseline to 12 months. A Fisher exact test was used to compare the proportion of patients in each treatment group who improved >4.5 in PedQL score from baseline to 6 and 12 months. A Fisher exact test was also used to compare the proportions of emergent AEs on treatment (analyzed as treatment-emergent AEs and emergent AEs leading to treatment withdrawal) between treatment groups. For all inferential analyses, no correction for multiplicity was applied.

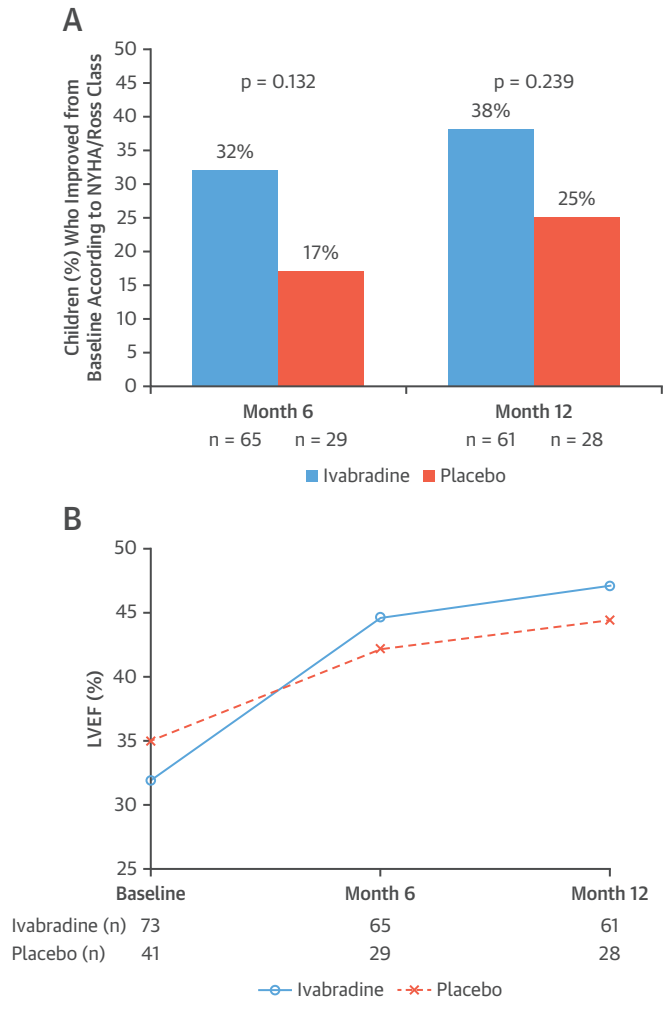
RESULTS

BASELINE CHARACTERISTICS. We enrolled 116 patients (n = 74 ivabradine; n = 42 placebo) with 17 children ages 6 to 12 months, 36 children ages >1 year and <3 years, and 63 children ages 3 to 18 years (Figure 1). More than three-quarters of the patients (77%) completed the study and 23 (20%) withdrew due to AEs. At inclusion (Table 1), the mean age was 5.8 ± 4.9 years. The majority (88%) of patients were Caucasian, and 55% were males. The mean resting heart rate in the whole population was 101 ± 20 beats/min; it was 131 ± 16 beats/min for children ages 6 to 12 months, 111 ± 11 beats/min for children ages >1 year and <3 years, and 87 ± 11 beats/min for children ages 3 to 18 years.

Patients had been diagnosed with chronic HF for 48.0 ± 49.7 months (ranging from 1 month to 16.7 years; median: 25.5 months). In 56% of patients, DCM was deemed idiopathic. Other causes of DCM were post-viral myocarditis (22%), LV noncompaction (19%), ischemia (2%), and post-anthracycline treatment (2%). Most (80%) were classified as NYHA functional class or Ross class II, and 16% and 4% were classified as class III and IV, respectively. Mean baseline LVEF was 32.9 ± 8.1% (ranging from 13.2% to 45.0%). Patients were treated concomitantly with various agents, with 94% on ACE inhibitors (Table 1). The NT-proBNP plasma concentration was 1,682 ± 3,224 pg/ml (geometric mean: 484 pg/ml). Overall, baseline characteristics were well-balanced between treatment groups.

HEART RATE REDUCTION AND DOSE. For all age groups combined, the primary endpoint (≥20% reduction of the baseline resting heart rate without bradycardia or symptoms of bradycardia) was reached by more children receiving ivabradine (70%) than placebo (12%) in the FAS population. The between-group comparison was statistically significant in

FIGURE 3 Functional Class and LVEF



(A) Although not significant, New York Heart Association (NYHA) or Ross functional class improved from baseline to 6 and 12 months to a greater degree with ivabradine. **(B)** Patients in the ivabradine group had a higher mean left ventricular ejection fraction (LVEF) by about 3 months after treatment.

favor of ivabradine (OR: 17.24; 95% CI: 5.91 to 50.30; $p < 0.0001$) (Table 2). Similar results were observed in the per-protocol population: among the 18 patients on ivabradine who did not reach the primary endpoint, 15 patients had a heart rate reduction of <20% at the highest dose, and 3 patients experienced asymptomatic bradycardia. Regardless of age, the effect of ivabradine upon resting heart rate was variable, with some patients reaching the primary endpoint at the lowest dose of ivabradine. Titration profiles varied markedly across patients. However, for most patients (32 [43%] in the ivabradine group), titration consisted of 4 steps of continuous dose increase. The mean doses of ivabradine during titration and the dose at the end of titration are described in Table 3 for children in the per-protocol population who reached the primary endpoint.

A large reduction in resting heart rate was observed between baseline and the end of the titration period with ivabradine from 102.0 ± 20.8 to 80.7 ± 19.8 beats/min versus 98.9 ± 18.2 beats/min to 97.5 ± 20.7 beats/min with placebo (Figure 2). The mean reduction was larger with ivabradine than with placebo (−21.2 ± 13.3 beats/min and −1.4 ± 11.5 beats/min, respectively in the FAS population) (Table 2). This between-group difference was statistically significant in favor of ivabradine (E ± SE: −18.99 ± 2.40; 95% CI: −23.75 to −14.23; $p < 0.0001$). Similar results were observed between baseline and 12 months and across all age groups, as well as in the per-protocol population.

SECONDARY OUTCOMES. An improvement in NYHA functional class or Ross class from baseline was observed in 32% of patients taking ivabradine versus 17% of patients taking placebo by 6 months ($p = 0.132$). Similar results were observed by 12 months (38% vs. 25%; $p = 0.239$) (Figure 3A). Most patients retained a stable NYHA functional class or Ross class whether in the ivabradine or placebo groups after 6 months (68% and 83%, respectively) and 12 months (62% and 75%, respectively). None of the patients had a worsening functional class. Similar trends were observed across all subgroups.

The mean overall patient LVEF increased during the study, with a greater change with ivabradine than placebo (13.5 ± 13.1% vs. 6.9 ± 11.4% at 12 months, respectively; E ± SE: 5.57 ± 2.44%; 95% CI: 0.75 to 10.40; $p = 0.024$) (Table 2, Figure 3B). The greater increase in LVEF with ivabradine was observed in all age subgroups, although statistical significance was not reached in any age class. The LV shortening fraction of children increased from baseline in both groups, with a larger increase with ivabradine than placebo (7.4 ± 7.7% vs. 2.7 ± 7.2% at 12 months, respectively; E ± SE: 4.08 ± 1.46%; 95% CI: 1.20 to 6.97; $p = 0.006$). Left ventricular end-systolic volume (LVESV) decreased from baseline in both groups, with a larger reduction with ivabradine than placebo (−16.2 ± 27 ml vs. −1.9 ± 17.9 ml, respectively at 12 months; E ± SE: −10.71 ± 4.26 ml; 95% CI: −19.15 to −2.26; $p = 0.013$). There was also a decrease in LV end-diastolic volume with ivabradine in comparison with baseline (−8.4 ± 34.1 ml), versus a slight increase with placebo (2.6 ± 26.3 ml); however, the mean difference between treatment was not significant (E ± SE: −7.91 ± 5.69 ml; 95% CI: −19.19 to 3.38; $p = 0.168$).

TABLE 4 Adverse Events

	Ivabradine (n = 73)	Placebo (n = 42)	Difference Between Group p Value
TEAE			
All	63 (86.3)	37 (88.1)	1.000
Infections and infestations	50 (68.5)	31 (73.8)	0.672
Investigations	21 (28.8)	16 (38.1)	0.310
Gastrointestinal	21 (28.8)	15 (35.7)	0.532
Eye disorders	9 (12.3)	6 (14.3)	0.780
Phosphenes	2 (2.7)	1 (2.4)	1.000
Cardiac disorders	11 (15.1)	13 (31.0)	0.057
Bradycardia*	8 (11)	1 (2.4)	0.152
Prolonged QTc interval†	6 (8)	7 (17)	0.223
Deaths	0	4 (9.5)‡	0.016
WEAE			
All	4 (5.5)	8 (19.1)	0.029
Prolonged QTc interval	3 (4.1)	3 (7.1)	0.667
Cardiac disorders	0	4 (9.5)§	0.016
Gastrointestinal disorders	0	1 (2.4)	NC‖
Heart transplant	1 (1.4)	2 (4.8)	0.25

Values are n (%). *Includes asymptomatic bradycardia, with symptomatic bradycardia reported only in the ivabradine group. Emergent bradycardia did not lead to withdrawal, but did lead to a dose reduction in 6 patients (1.6%). †None of the emergent QTc prolongations were either serious or symptomatic in the ivabradine group. ‡1 septic shock, 1 sudden cardiac arrest, 1 ventricular tachycardia, and 1 ventricular fibrillation. §1 atrial flutter, 1 worsening of chronic heart failure, 1 cardiogenic shock, and 1 low cardiac output syndrome. ‖p value not calculated in view of the small number of patients.

NC = not calculated; TEAE = treatment-emergent adverse events; WEAE = emergent adverse events leading to treatment withdrawal.

A similar and substantial decrease in NT-proBNP was observed in both the ivabradine and placebo groups between baseline and 12 months. The decreases were −710 ± 1,478 pg/ml (median −128 pg/ml) with ivabradine and −367 ± 576 pg/ml (median −129 pg/ml) with placebo.

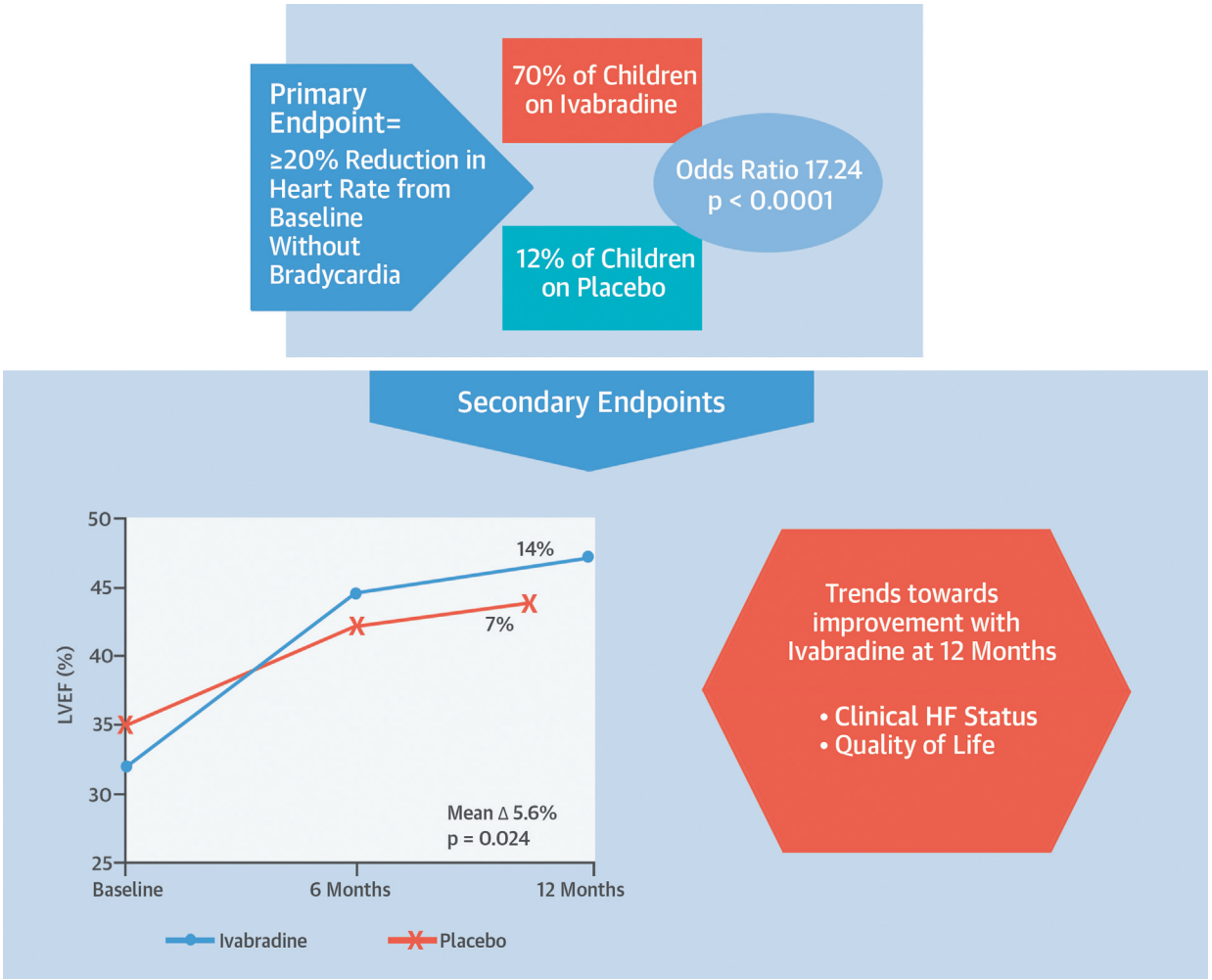
QUALITY OF LIFE. A total of 69 patients were included in the QOL substudy (n = 44 ivabradine; n = 25 placebo). QOL was evaluated by the parents (n = 36 ivabradine; n = 19 placebo) and/or by the children themselves (n = 17 ivabradine; n = 11 placebo). At baseline, the total score was similar in both treatment groups (parent-reported: 67.4 ± 19.2 with ivabradine vs. 69.6 ± 14.8 with placebo; child-reported: 71.3 ± 14.1 vs. 70.0 ± 9.9, respectively). The parent questionnaires showed an improvement in total score in favor of ivabradine at 6 months and a trend in improvement at 12 months (Table 2). The children's questionnaires did not show any relevant change during the study or any between-group difference (p = 0.71 at 12 months). By 6 months, the assessments reported by the parents showed an improvement of >4.5 in the PedQL total scale score in 59% of children on ivabradine and in 47% of children on placebo (Table 2); similar results were observed at 12 months.

SAFETY. The overall safety of ivabradine was comparable to the placebo group. Adverse events were reported at a similar frequency in both treatment groups (86% with ivabradine vs. 88% with placebo) (Table 4). The most frequently affected system organ classes were infections and infestations (mainly nasopharyngitis, bronchitis, upper respiratory tract infection, and viral infection), and gastrointestinal disorders (mainly gastroenteritis, diarrhea, and vomiting), with a lower frequency of AEs with ivabradine than placebo. A prolonged QTc interval was observed less frequently with ivabradine than placebo (8% vs. 17%), and led to study withdrawal in 4% and 7% of patients, respectively. None of the emergent QTc prolongations in the ivabradine group were serious or symptomatic. Phosphenes were reported at a similar frequency in both groups. None of the patients reported blurred vision. Globally, cardiac concerns were reported less frequently by patients on ivabradine than placebo (15% vs. 31%, respectively), and led to withdrawal in the placebo group only. Bradycardia—asymptomatic cases included—was reported with a higher frequency with ivabradine than placebo (11.0% vs. 2.4%). Symptomatic bradycardia was reported in the ivabradine group only: 4% in the age >1 year and <3 years subgroup and 5% in the age 3 to 18 years subgroup. Emergent bradycardia led to a dose reduction in 6 patients (1.6%), all with ivabradine, none of which led to study withdrawal. No patient died in the ivabradine group, but 4 patients (9.5%) died in the placebo group (between-group difference: p = 0.016) (Table 4). A total of 3 heart transplants were performed (2.5%): 1 in the ivabradine group and 2 in the placebo group. Additionally, 1 patient on ivabradine underwent a heart transplant 2 months after the last study drug intake.

DISCUSSION

In children with DCM and symptomatic chronic HF, adding ivabradine to stable HF therapy (including beta-blockers) could reduce heart rate by more than 20% in a clear majority of children without inducing bradycardia. Ivabradine showed similar efficacy for reducing heart rate in a wide range of age classes, from 6 months to 18 years (Central Illustration). We observed a high interindividual variability in response to ivabradine, indicating that dose titration is important—and should be mandatory—when used to treat children with chronic HF. Ivabradine treatment was associated with significant improvement in LVEF (+14%) and LVESV (−16.2 ± 27.0 ml) at 12 months, greater than that seen with placebo (+7% and −1.9 ml for LVEF and LVESV, respectively). In line with this

CENTRAL ILLUSTRATION **Ivabradine in Children With Dilated Cardiomyopathy**



Bonnet, D. et al. J Am Coll Cardiol. 2017;70(10):1262–72.

This randomized, double-blind, placebo-controlled trial explored the dose-response relationship of ivabradine in children with dilated cardiomyopathy and symptomatic chronic heart failure (HF). The primary endpoint (reduction of ≥20% of heart rate from baseline without bradycardia) was reached in a significantly higher proportion in the treatment arm. As to secondary endpoints, significant improvement of left ventricular ejection fraction (LVEF) was significantly better in the treatment arm; the other secondary endpoints were not significantly different but trended towards improvement with ivabradine.

improvement in cardiac function, children tended to have better clinical status and QOL when treated with ivabradine compared with placebo.

Current recommendations for treatment of chronic HF in children are frequently extrapolated from adult clinical trials, and most of the widely used management strategies involve off-label prescription. There are currently few pediatric formulations available in HF, and evidence-based data are scarce (5,12,27,28). Our study was the first randomized, placebo-controlled trial of ivabradine in children with DCM and symptomatic chronic HF. Our findings were broadly consistent with the beneficial effects of ivabradine demonstrated in adults, and with 2 anecdotal cases of adolescents with DCM in whom LVEF improved after treatment with ivabradine 7.5 mg twice daily (29).

In terms of safety, ivabradine was well-tolerated and safe for use in this study. There were no serious bradycardic events. However, the lack of bradycardic events might reflect the careful supervision of a structured titration period, supporting the notion that a titration period should be considered mandatory in children. It remains important to monitor

heart rate at follow-up when treating chronic HF in children with DCM who are taking ivabradine. The rates of known AEs with ivabradine, such as phosphenes and bradycardia, were in line with the rates observed in adults (16). QTc prolongations were less frequent with ivabradine than placebo. The results of the pharmacokinetic and pharmacodynamic analysis showed that the relationship described in adults was conserved in the pediatric population (19,20).

The majority of patients in this study were treated with combinations of recommended drugs (ACE inhibitors [94%], beta-blockers [76%], aldosterone antagonists [79%], and digitalis [50%]) (8,30,31), and had stable chronic HF with a long history of DCM. As such, worsening events were infrequent, as shown by the limited number of heart transplantation and/or deaths in both groups. Although improvement and normalization might occur in 20% of these patients (5), this is mainly observed by 24 months after diagnosis of DCM. For these reasons, we consider that the observed trends in clinical status and QOL, although not statistically significant, might be clinically important. Our results suggested that using ivabradine as an add-on therapy to standard of care therapy in children with chronic HF due to DCM might be beneficial and deserves further investigation.

STUDY LIMITATIONS. Attainment of the primary endpoint (heart rate reduction) alone did not prove that ivabradine is efficacious in treating children with DCM and HF. This study was not powered to demonstrate a mortality advantage, and did not attempt to demonstrate a combined endpoint effect for treatment with ivabradine. Data demonstrating efficacy on morbidity and mortality are more compelling, but require very large numbers of patients, which is unrealistic in pediatric HF.

This study, as is frequently the case for pediatric HF, was limited by the number of patients available for recruitment, as pediatric DCM is an uncommon disease. However, in comparison to other studies of this kind, our study population could be considered relatively robust, with an adequate length of follow-up. Other limitations inherent in this patient population included the tendency to see an increase in LVEF over time, as was noted in the Pediatric Carvedilol Trial (32), and the difficulty in defining surrogate endpoints for a lack of improvement over time.

Numerous surrogate endpoints used in adult studies of HF, such as hospitalization for HF, exercise capacity, QOL, LVEF, or NT-proBNP, have inherent difficulties in children, and are therefore not always useful to demonstrate the efficacy of add-on therapy combined with standard care. Nonetheless, in this small study, we were encouraged to see significant improvement (LVEF) or trends in improvement (HF class, QOL) in most of these indicators, and we feel that an efficacy study of ivabradine in pediatric HF may well be warranted.

CONCLUSIONS

Ivabradine has a good safety profile and was associated with a significant reduction in resting heart rate of children with chronic HF and DCM in all age subgroups tested from 6 months to 18 years. Children treated with ivabradine also showed significant improvement in echocardiographic indexes (LVEF and LVESV) and a favorable trend for clinical status and QOL compared with placebo. Importantly, this study provided more data on the efficacy and safety of treating children with DCM and chronic HF with ivabradine and highlighted the importance of a titration period. Further pediatric studies such as this are required to enable physicians to make evidence-based decisions in the management of pediatric heart failure patients.

ACKNOWLEDGMENTS This paper was prepared with medical writing assistance from Nichola O'Looney Mazo, PhD (Servier, France). Scientific Board: D. Bonnet, F. Berger, E. Jokinen, P.F. Kantor, and P.E.F. Daubeney. Participating investigators (who included at least 1 patient) and number of included patients per country: Belgium (n = 1): M. Gewillig. Brazil (n = 13): E.S.K. Horowitz, J.Y. Afiune, E. Atik, K.M.P Castello Branco, and M.V.T Santana. Bulgaria (n = 6): M. Tzonzarova, M. Bosheva, and L. Marinov. Finland (n = 3): J. Pihkala and A. Arola. France (n = 16): D. Bonnet, P. Amedro, A. Fraisse, and J.-B. Thambo. Germany (n = 11): O. Miera, H. Abdul-Khaliq, N. Haas, R. Kozlik-Feldmann, B. Stiller, and S. Dittrich. Hungary (n = 2): A. Szatmari. Italy (n = 8): G. Pongiglione, M. Bonvicini, and G. Pacileo. Mexico (n = 2): J.E. Calderon-Colmenero and H. Osnaya. Poland (n = 13): W. Kawalec, J. Kusa, and R. Sabiniewicz. Portugal (n = 9): F. Pinto, R. Anjos, and A. Marinho. Romania (n = 6): R. Toganel and C.C. Olteanu. Russia (n = 17): M. Shkolnikova, E. Basargina, S. Ivanov, and S. Lebedkova. Spain (n = 5): C. Medrano, D. Albert Brotons, S. Cesar Diaz, F. Rueda Nuñez, and E. Gomez Guzman. Sweden (n = 3): H. Wahlander and T. Higgins. United Kingdom (n = 1): P.E.F. Daubeney.

ADDRESS FOR CORRESPONDENCE: Dr. Damien Bonnet, Cardiologie Congénitale et Pédiatrique, Hôpital Necker Enfants Malades, 149 rue de Sevres, 75015 Paris, France. E-mail: damien.bonnet@aphp.fr.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Because the heart rate response varies in pediatric patients with chronic HF receiving combination therapy with beta-blockers, the dose of ivabradine must often be uptitrated to achieve improvement in clinical status and LV systolic function.

TRANSLATIONAL OUTLOOK: Large trials of pediatric patients with heterogeneous phenotypes are needed to assure the generalizability of data from pharmacological studies across the wide array of children with acute and chronic HF.

REFERENCES

1. Wittlieb-Weber CA, Lin KY, Zaoutis TE, et al. Pediatric versus adult cardiomyopathy and heart failure-related hospitalizations: a value-based analysis. J Card Fail 2015;21:76–82.

2. Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003;348:1647–55.

3. Nugent AW, Daubeney PE, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 2003;348:1639–46.

4. Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 2006;296:1867–76.

5. Everitt MD, Sleeper LA, Lu M, et al. Recovery of echocardiographic function in children with idiopathic dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. J Am Coll Cardiol 2014;63:1405–13.

6. Alexander PM, Daubeney PE, Nugent AW, et al. Long-term outcomes of dilated cardiomyopathy diagnosed during childhood: results from a national population-based study of childhood cardiomyopathy. Circulation 2013;128:2039–46.

7. Lipshultz SE, Cochran TR, Briston DA, et al. Pediatric cardiomyopathies: causes, epidemiology, clinical course, preventive strategies and therapies. Future Cardiol 2013;9:817–48.

8. Kantor PF, Lougheed J, Dancea A, et al. Presentation, diagnosis, and medical management of heart failure in children: Canadian Cardiovascular Society guidelines. Can J Cardiol 2013;29:1535–52.

9. Kirk R, Dipchand AI, Rosenthal DN, et al. The International Society for Heart and Lung Transplantation Guidelines for the management of pediatric heart failure: executive summary [corrected]. J Heart Lung Transplant 2014;33:888–909.

10. Kay JD, Colan SD, Graham TP Jr. Congestive heart failure in pediatric patients. Am Heart J 2001;142:923–8.

11. Balfour I. Management of chronic congestive heart failure in children. Curr Treat Options Cardiovasc Med 2004;6:407–16.

12. Shaddy RE, Boucek MM, Hsu DT, et al. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. JAMA 2007;298:1171–9.

13. Pocock SJ, Wang D, Pfeffer MA, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J 2006;27:65–75.

14. Katz AM. The myocardium in congestive heart failure. Am J Cardiol 1989;63:12A–6A.

15. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. Am J Cardiol 2008;101:865–9.

16. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled trial. Lancet 2010;376:875–85.

17. McMurray JJ, Adamopoulos S, Anker SD, et al., for the ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

18. Ross RD, Bollinger RO, Pinsky WW. Grading the severity of congestive heart failure in infants. Pediatr Cardiol 1992;13:72–5.

19. Peigne S, Bouzom F, Brendel K, Gesson C, Fouliard S, Chenel M. Model-based approaches for ivabradine development in paediatric population, part I: study preparation assessment. J Pharmacokinet Pharmacodyn 2016;43:13–27.

20. Peigne S, Fouliard S, Decourcelle S, Chenel M. Model-based approaches for ivabradine development in paediatric population, part II: PK and PK/PD assessment. J Pharmacokinet Pharmacodyn 2016;43:29–43.

21. Rijnbeek PR, Witsenburg M, Schrama E, Hess J, Kors JA. New normal limits for the paediatric electrocardiogram. Eur Heart J 2001;22:702–11.

22. Delgizzi LJ, Ueda JN. Using inotropic and vasodilating agents in pediatric patients with cardiac disease. AACN Clin Issues Crit Care Nurs 1990;1:131–47.

23. Veldman A, Rupp S, Schranz D. New inotropic pharmacologic strategies targeting the failing myocardium in the newborn and infant. Mini Rev Med Chem 2006;6:785–92.

24. Bohm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 2010;376:886–94.

25. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care 2001;39:800–12.

26. The Medical Dictionary for Regulatory Activities. Available at: https://www.meddra.org/. Accessed July 20, 2017.

27. Frobel AK, Hulpke-Wette M, Schmidt KG, Laer S. Beta-blockers for congestive heart failure in children. Cochrane Database Syst Rev 2009:CD007037.

28. Di Filippo S. Beta-adrenergic receptor antagonists and chronic heart failure in children. Ther Clin Risk Manag 2007;3:847–54.

29. Parsons S, Clark AL, Cleland JG. The remarkable effect of ivabradine in two adolescents with dilated cardiomyopathy. Clin Res Cardiol 2014;103:847–9.

30. Rosenthal D, Chrisant MR, Edens E, et al. International Society for Heart and Lung Transplantation: practice guidelines for management of heart failure in children. J Heart Lung Transplant 2004;23:1313–33.

31. Rossano JW, Shaddy RE. Update on pharmacological heart failure therapies in children: do adult medications work in children and if not, why not? Circulation 2014;129:607–12.

32. Huang M, Zhang X, Chen S, et al. The effect of carvedilol treatment on chronic heart failure in pediatric patients with dilated cardiomyopathy: a prospective, randomized-controlled study. Pediatr Cardiol 2013;34:680–5.

KEY WORDS heart rate, left ventricular ejection fraction, N-terminal pro-B-type natriuretic peptide, pediatric, quality of life