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RAPID COMMUNICATIONS

A randomized controlled trial of eplerenone in asymptomatic phospholamban p.Arg14del carriers

Remco de Brouwer [1,2†], Wouter P. te Rijdt [1,2,3†‡], Edgar T. Hoorntje [2,4], Ahmad Amin[5,6‡], Folkert W. Asselbergs [5,6,7,8], Moniek G.P.J. Cox[1], Jeroen F. van der Heijden[7,9], Hans Hillege [1], Jacco C. Karper[1], Belend Mahmoud[1], Peter van der Meer[1], Anton Oomen[10], Anneline S.J.M. te Riele[7‡], Herman H.W. Silljé[1], Hanno L. Tan [2,5,6‡], Jan Peter van Tintelen[2,11‡], Dirk J. van Veldhuisen [1], Berend Daan Westenbrink[1], Ans C.P. Wiesfeld[1], Tineke P. Willems[12], Paul A. van der Zwaag[4], Arthur A.M. Wilde [5,6‡], Rudolf A. de Boer [1,13], and Maarten P. van den Berg [1]

[1]Department of Cardiology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands; [2]Netherlands Heart Institute, Utrecht, the Netherlands; [3]Department of Genetics, Erasmus University Medical Centre, Rotterdam, the Netherlands; [4]Department of Genetics, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands; [5]Department of Cardiology, Amsterdam UMC location University of Amsterdam, Amsterdam, the Netherlands; [6]Amsterdam Cardiovascular Sciences, Heart Failure and Arrhythmias, Amsterdam, the Netherlands; [7]Department of Cardiology, Division Heart & Lungs, Utrecht University Medical Centre, Utrecht, the Netherlands; [8]Institute of Cardiovascular Science and Institute of Health Informatics, Faculty of Population Health Sciences, University College London, London, UK; [9]Department of Cardiology, Haga Teaching Hospital, The Hague, the Netherlands; [10]Department of Cardiology, Antonius Hospital, Sneek, the Netherlands; [11]Department of Genetics, University of Utrecht, Utrecht University Medical Centre, Utrecht, the Netherlands; [12]Department of Radiology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands; and [13]Department of Cardiology, Erasmus University Medical Centre, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands

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Introduction

Phospholamban (*PLN*; p.Arg14del) cardiomyopathy is an inherited disease caused by the pathogenic p.Arg14del variant in the *PLN* gene. Clinically, it is characterized by malignant ventricular arrhythmias and progressive heart failure.[1,2] Cardiac fibrotic tissue remodelling occurs early on in *PLN* p.Arg14del carriers.[3,4] Eplerenone was deemed a treatment candidate because of its beneficial effects on ventricular remodelling and antifibrotic properties.[5,6] We conducted the multicentre randomized trial '*i*ntervention in *PHO*spholamban *RE*lated *CA*rdiomyopathy *ST*udy' (i-PHORECAST) to assess whether treatment with eplerenone of asymptomatic *PLN* p.Arg14del carriers attenuates disease onset and progression.

Methods

Study design

The i-PHORECAST was a clinical trial following the prospective, randomized, open, blinded endpoint design[7] and registered in the clinicaltrials.gov-register (registration number: NCT01857856). The i-PHORECAST design manuscript has been published previously.[8]

* Corresponding author. Email: r.a.deboer@erasmusmc.nl
† Both authors contributed equally.
‡ Member of the European Reference Network (ERN) for rare, low prevalence, and complex diseases of the heart: ERN GUARD-Heart (ERN GUARDHEART; http://guardheart.ern-net.eu).

Table 1 Baseline and end of study characteristics, endpoint distribution

Baseline characteristics	Total ($n = 84$)	Eplerenone ($n = 42$)	Control ($n = 42$)	Missing, *n* (%)	*P*-value
Age at inclusion, years [IQR]	39 [27–50]	40 [29–49]	39 [24–51]	-	-
Male sex, *n* (%)	37 (44)	18 (43)	19 (45)	-	-
Body mass index, kg/m^2 [IQR]	25 [23–28]	25 [23–29]	25 [22–27]	-	-
Systolic blood pressure, mmHg [IQR]	122 [110–134]	126 [115–136]	120 [110–130]	-	-
Diastolic blood pressure, mmHg [IQR]	75 [66–80]	75 [70–80]	74 [65–84]	-	-
PVCs/24 h, *n* [IQR]	9 [1–61]	9 [1–30]	12 [0–77]	-	-
QRS amplitude, mV [IQR]	23 [18–28]	24 [18–31]	22 [17–27]	-	-
PR duration, ms [IQR]	142 [132–160]	142 [135–159]	143 [126–159]	-	-
QRS duration, ms [IQR]	85 [80–94]	85 [80–94]	86 [78–94]	-	-

Baseline CMR characteristics[a]	Total ($n = 74$)	Eplerenone ($n = 37$)	Control ($n = 37$)	Missing, *n* (%)	*P*-value
LVEDV, mL [IQR]	154 [136–175]	158 [139–171]	153 [132–181]	-	-
LVEF, % [IQR]	60 [56–62]	60 [57–62]	59 [56–61]	-	-
RVEDV, mL [IQR]	178 [151–204]	178 [159–188]	175 [146–207]	-	-
RVEF, % [IQR]	51 [49–55]	52 [50–55]	50 [48–55]	-	-
LGE, *n* (%)	14 (17)	9 (21)	5 (12)	4 (5)	-

End of study characteristics	Total ($n = 84$)	Eplerenone ($n = 42$)	Control ($n = 42$)	Missing, *n* (%)	*P*-value
Composite endpoint reached	56 (67)	27 (64)	29 (69)	-	0.817
PVCs/24 h, *n* [IQR]	6 [1–123]	11 [2–91]	5 [1–131]	1 (1)	0.673
QRS amplitude, mV [IQR]	23 [17–29]	23 [19–29]	24 [16–29]	2 (2)	0.992
PR duration, ms [IQR]	144 [130–160]	144 [130–157]	146 [132–160]	2 (2)	0.606
QRS duration, ms [IQR]	88 [80–96]	88 [80–96]	86 [80–95]	2 (2)	0.723

End of study CMR characteristics[a]	Total ($n = 74$)	Eplerenone ($n = 37$)	Control ($n = 37$)	Missing, *n* (%)	*P*-value
LVEDV, mL [IQR]	150 [129–168]	146 [134–165]	153 [126–175]	-	0.996
LVEF, % [IQR]	59 [55–61]	57 [55–60]	60 [55–62]	-	0.171
RVEDV, mL [IQR]	169 [144–191]	167 [149–183]	174 [140–204]	-	0.638
RVEF, % [IQR]	50 [49–54]	51 [49–53]	50 [49–54]	-	0.709
LGE, *n* (%)	22 (26)	12 (29)	10 (24)	4 (5)	0.797

[a]All percentages are calculated using a total cohort size of 84 and a group size of 42. PVCs, premature ventricular contractions.

Carriers without symptoms were selected from the national *PHO*spholamban *RE*lated *CA*rdiomyopathy *ST*udy (PHORECAST) registry (https://www.phorecast.nl/), which collected all *PLN* p.Arg14del carriers known at the time of study inception ($n = 436$). At an initial screening visit, asymptomatic status was verified.

Study population

Study participants were 18 to 65 years of age, genotype-confirmed *PLN* p.Arg14del carriers, and asymptomatic: no cardiac symptoms, New York Heart Association class I, a left ventricular ejection fraction (EF) measured with cardiac magnetic resonance imaging (CMR) of $\geq 45\%$, no diagnosis of dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, no treatment with cardioactive medication at inclusion, no history of (non-)sustained ventricular tachycardia or fibrillation, ≤ 2500 premature ventricular contractions (PVCs) during 24-h Holter monitoring, no evidence of ischaemic heart disease, and no history of hyperkalaemia, severe renal dysfunction, or hepatic impairment. Additionally, pregnant women, women pregnant during the 60 days before potential inclusion, and women planning on becoming pregnant were excluded from the trial.

Intervention and clinical evaluation

Study participants were randomized 1:1 to receive either 50 mg of eplerenone once daily or no treatment. The follow-up duration was 3 years. Twelve-lead electrocardiogram (ECG), 24-h three-channel Holter registration, exercise testing, physical examination, medical history and event review, and venous blood analysis were performed yearly and assessed by experienced cardiologists. Cardiac magnetic resonance imaging was performed at baseline and at the end of follow-up (3 years).

Composite primary endpoint

The composite primary endpoint consisted of: a ≥10% increase in left and/or right ventricular end-diastolic volume (L/RVEDV), a ≥5% decrease in left and/or right ventricular EF (L/RVEF), new development of late gadolinium enhancement (LGE) as a measure of cardiac fibrosis, a ≥100% increase and absolute increase of ≥1000 PVCs on Holter registration, development of non-sustained ventricular tachycardia, a decrease in QRS voltage on ECG of ≥25%, development of cardiac symptoms necessitating treatment, and cardiovascular death. New development of LGE was defined as LGE observed in participants whose initial CMR did not contain LGE. A blinded committee adjudicated the endpoints.

Statistical analyses

Continuous data are given as medians (interquartile range; IQR). Categorical values are given as absolute values (%). All percentages provided are calculated using a cohort size of $n = 84$ and a group size of $n = 42$ unless stated otherwise. Dichotomous variables were compared using the χ^2 test. Continuous variables were compared using the Kruskal–Wallis test. Sample size estimation was based on the prediction that 50% of asymptomatic *PLN* p.Arg14del carriers would reach the primary endpoint within 3 years and a predicted treatment effect of eplerenone of 50%. To ensure 80% power at a 0.05 significance level with an assumed 15% loss to follow-up during the study, a required cohort size of 150 study participants (75 in each group) was estimated.

Results

From May 2014 until January 2018, 84 carriers from the initial selection of 436 p.Arg14del *PLN* carriers were enrolled, which was markedly lower than the target number of participants (150), resulting in an underpowered sample size. In total, paired CMR data of sufficient quality was available of 74 out of 84 carriers, 37 in both the eplerenone group and the control group. Characteristics of the total cohort at baseline and at end of study are listed in *Table 1*. There were no statistically significant differences between the groups.

Median age at inclusion was 39 years (Q1–Q3: 27–50 years), 37 (44%) people were male. After 3 years follow-up, 56/84 (67%) people showed evidence of disease progression by reaching the composite endpoint, 29/42 (69%) in the control group and 27/42 (64%) in the eplerenone group ($P = 0.817$). The two components of the primary endpoint that were most often reached were a decrease in left ventricular EF (29/84, 35%) and/or right ventricular EF by ≥5% (24/84, 29%), followed by the combination of non-sustained ventricular tachycardia and increase in PVC count on Holter monitoring (14/84, 17%).

In total, 14/84 (17%) people already showed some LGE at baseline despite their asymptomatic status, 9/42 (21%) in the eplerenone group and 5/42 (12%) in the control group ($P = 0.520$). Out of 10 carriers with newly observed LGE at the end of the study, a decrease in ventricular function or an increase in ventricular volume was observed in five.

No sustained ventricular tachycardia was observed during the trial. Sporadic QRS amplitude decrease was observed, but no newly developed low voltage ECGs were observed. Eplerenone was well-tolerated with no significant difference in the occurrence of adverse events between the groups.

Discussion

Within the 3-year duration of i-PHORECAST trial, disease progression, i.e. reaching the composite endpoint, was observed in two-thirds of participants, both in members of the eplerenone and control groups. Moreover, signs of *PLN* p.Arg14del cardiomyopathy were already present at baseline, in particular LGE, despite the asymptomatic status of participants. These findings provide a novel perspective regarding *PLN* p.Arg14del cardiomyopathy. Given the fact that the sample size was smaller than expected, conclusions from this study must be drawn with caution, particularly regarding the effect of eplerenone. Although no signal for such an effect was observed, we cannot exclude that with the intended sample size this might have been observed. There was no evidence of an effect of treatment with eplerenone based on this analysis. Eplerenone itself was safe and well-tolerated. Future research into *PLN* p.Arg14del cardiomyopathy disease progression or modification—and more broadly, research into asymptomatic carriers of pathogenic variations associated with genetic cardiomyopathies—may be better designed using the knowledge obtained in this study.

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Data availability

The data underlying this article cannot be shared publicly due to concerns regarding the privacy of individuals who participated in the study. The data, or a subset thereof, will be shared on reasonable request to the corresponding author.

Conflict of interest

R.A.d.B. is president-elect of the Dutch Cardiac Society (NVVC), member of the Executive Committee of the DELIVER-trial and has received grants from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals GmbH, Ionis Pharmaceuticals, Inc., Novo Nordisk, and Roche in the last 36 months. R.A.d.B. has received payment or honoraria from Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis, and Roche in the last 36 months. J.P.v.T. has received consulting fees from StrideBio in the last 36 months. A.A.M.W. has received grants from the Dutch Heart Foundation and consulting fees from LQT Therapeutics and ARMGO in the last 36 months. A.A.M.W. additionally is a member of the advisory board of the Leap Trial.

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