ORIGINAL ARTICLE

WILEY

Assessment of ECG during hybrid comprehensive telerehabilitation in heart failure patients—Subanalysis of the Telerehabilitation in Heart Failure Patients (TELEREH-HF) randomized clinical trial

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Abstract

Background: Exercise training in heart failure (HF) patients should be monitored to ensure patients' safety. Electrocardiographic (ECG) telemonitoring was used to assess the safety of hybrid comprehensive telerehabilitation (HCTR).

Objective: Analysis of ECG recorded during HCTR in HF patients.

Methods: The TELEREH-HF multicenter, randomized, controlled trial enrolled 850 HF patients with New York Heart Association class I-III and left ventricular ejection fraction of ≤40%. This subanalysis focuses on 386 patients (aged 62 ± 11 years, LVEF 31 ± 7%) randomized to HCTR. HCTR was telemonitored with a device allowing to record 16-s fragments of ECG and to transmit the data via mobile phone network to the monitoring center.

Results In 386 patients, 16,622 HCTR sessions were recorded and 66,488 ECGs fragments were evaluated. Sinus rhythm was present in 320 (83%) and permanent atrial fibrillation (AF) in 66 (17%) patients, respectively. The most common arrhythmias were ventricular and atrial premature beats, recorded in 76.4% and 27.7% of the patients, respectively. Non-sustained ventricular tachycardia (21 episodes in 8 patients) and paroxysmal AF episodes (6 in 4 patients) were rare. None of the analyzed demographic and clinical characteristics was predictive for onset of the new arrhythmias on exercise.

Conclusion: Telerehabilitation in HF patients was safe without the evidence for symptomatic arrhythmias requiring discontinuation of telerehabilitation. Only one mildly symptomatic paroxysmal AF episode led to the short-term suspension of the training program. The most common arrhythmias were atrial and ventricular premature beats. These arrhythmias did not result in any changes in rehabilitation and therapy regimens.

KEYWORDS

arrhythmia, cardiac telerehabilitation, ECG monitoring, heart failure

1 | INTRODUCTION

All clinically stable heart failure (HF) patients should be enrolled in an exercise-based cardiac rehabilitation program with a multi-faceted approach (Ambrosetti et al., 2020; Ponikowski et al., 2016; Seferovic et al., 2019). Telemedicine offers a novel approach to organize and implement the comprehensive management of HF patients including the possibility of tele-supervised exercise training (Piotrowicz et al., 2020). Home-based cardiac telerehabilitation is feasible as it uses technology-based telemedicine programs. Recently, hybrid comprehensive telerehabilitation (HCTR) became increasingly important during the COVID-19 pandemic, where self-managed home-based interventions are encouraged. As per recommendations, exercise training in HF patients should be monitored to ensure patients' safety (Fletcher et al., 2013; Piepoli et al., 2011; Piotrowicz et al., 2012). Electrocardiographic (ECG) monitoring, besides arrhythmia and ischemia evaluation, allows the assessment of the heart rate range during the training session. These variables guide the adjustment of the level of the exercise intensity, which determines the effectiveness of rehabilitation program. Therefore, high-risk patients, including HF patients, should be medically supervised with ECG monitoring (Fletcher et al., 2013; Piepoli et al., 2011; Piotrowicz et al., 2012). These standards apply to inpatient and outpatient (e.g., in outpatient centers) cardiac rehabilitation monitoring (Ambrosetti et al., 2020; Ponikowski et al., 2016; Seferovic et al., 2019). However, they do not address the specific forms and methods of ECG monitoring during cardiac telerehabilitation. The optimal forms of ECG monitoring (real-time or sequential monitoring) during home-based telemonitored cardiac rehabilitation are still under discussion.

Our study from 2012 was a pioneering single-center study that evaluated sequential ECG monitoring during home-based telemonitored cardiac rehabilitation of 75 HF patients (Piotrowicz et al., 2012). Therefore, in this substudy of the TELEREH-HF trial we sought to investigate the safety of telerehabilitation measured by the frequency of cardiac arrhythmias during telerehabilitation in HF patients. TELEREH-HF trial is the largest multicenter, prospective, randomized clinical study to date that assessed a 9-week HCTR intervention in HF patients compared with usual care, and had the largest collection of ECG recordings during telerehabilitation.

2 | METHODS

The TELEREH-HF study (Clinical Trials.gov NCT 02523560) enrolled clinically stable HF patients with New York Heart Association (NYHA) class I, II, or III and left ventricular ejection fraction (LVEF) of 40% or less after a hospitalization due to worsening HF within 6 months prior to randomization (Piotrowicz et al., 2019, 2020). The trial was designed to determine whether potential improvements in functional and quality-of-life outcomes after 9-week training period translate into improvement into clinical outcomes during the extended follow-up of 12 to 24 months (Piotrowicz et al., 2019, 2020). The study conduct was guided by good clinical practice, in accordance with the Declaration of Helsinki and the regulations applicable in Poland. The trial was approved by the local ethics committee (Local Bioethical Commission at the National Institute of Cardiology, Warsaw, Poland). Each patient provided written informed consent.

Between June 8, 2015, and June 28, 2017, 850 eligible patients were randomized in a 1:1 ratio to either a HCTR plus usual care group (HCTR group) or a usual care only (UC group). The inclusion and exclusion criteria have been presented elsewhere in study design paper (Piotrowicz et al., 2019). The patient in the HCTR group underwent a 9-week HCTR program consisting of two stages: an initial stage (1 week) conducted in hospital and the subsequent stage (8 weeks) of home-based HCTR 5 times weekly. The telerehabilitation program encompassed three training modalities: endurance aerobic Nordic walking training, respiratory muscle training, light resistance, and strength exercises. A detailed description of the intervention has been published elsewhere (Piotrowicz et al., 2019).

2.1 | ECG telemonitoring and exercise training

The telemonitoring system included a special remote device for supervised exercise training (a telerehabilitation set), which consisted of an EHO-MINI device (Pro Plus Company, Poland), a blood-pressure-measuring device, and a weighing scale; data transmission set via a mobile telephone; and a monitoring center capable of receiving and storing patients' medical data. HCTR was telemonitored with an EHO-MINI device recording 16-s ECG recordings (from three precordial leads) and transmitting ECG data via mobile phone network to the monitoring center. The device had training sessions preprogrammed individually for each patient with defined exercise duration and breaks (Piotrowicz et al., 2019, 2020). Before beginning training sessions, patients performed preliminary examinations (blood pressure, body weight measurement), answered a questionnaire regarding the present health condition, and then transmitted resting ECG to the monitoring center. Afterward, the medical staff in the monitoring center assessed the patients' ability to proceed safely and gave consent to each training session if no contraindications were identified (Piotrowicz et al., 2019). The contraindication to begin the training session included symptoms suggesting decompensation of heart failure (e.g., dyspnea, 1.8 kg or more increase in body mass over the previous 1–3 days), uncontrolled hypertension or new onset of symptomatic atrial fibrillation/atrial flutter, symptomatic complex ventricular arrhythmia at rest, supine resting heart above 100 b.p.m., and grade 2 and 3 atrioventricular block (Piepoli et al., 2011). During the training session, the device notified the patient about the current task to perform (exercise, ECG, rest) via sound (bleeps) and light signals (colors emitting diodes).

We used the sequential ECG monitoring method. The timings of automatic ECG recordings were pre-set and coordinated with exercise training. The EHO-MINI device was preprogrammed to record four 16-s ECGs during the one training session.

The first ECG was obtained as a part of the preliminary examination before training, the next 3 during the exercise training, each at the end of the prespecified training interval. If the training session was completed, the ECG recordings were immediately automatically transmitted to the monitoring center after the end of every training session. On the basis of the obtained data, medical teams were able to adjust the training workload appropriately for subsequent training sessions.

2.2 | Measures

Taking the data from the ECG recordings, we focused primarily on incidence and type of cardiac arrhythmias at rest and during training sessions in term of HCTR safety.

We also analyzed newly appearing arrhythmias on exercise depending on the demographic and clinical characteristics comparing two groups: patients with no arrhythmias at rest and on exercise and patients with no arrhythmias at rest and with newly appearing arrhythmias on exercise.

In univariable analyses, 9 demographic and clinical factors (gender, age, basic cardiac rhythm, HF etiology, New York Heart Association [NYHA] functional class, N-terminal fragments of B-type natriuretic peptide level [NT-proBNP], left ventricular ejection fraction [LVEF], delta [Δ] in peak oxygen consumption [pVO2], presence/absence of diabetes mellitus) were considered.

Additionally, we assessed the percentage of training sessions with the target training heart rate (ttHR) achieved. Cardiopulmonary exercise testing at baseline was used to set intensity for exercise during training sessions. The intensity of Nordic walking training for HCTR population was calculated as 40%–70% of heart rate reserve or reaching a score of 11–12 on the Borg Rating of Perceived Exertion Scale (Piotrowicz et al., 2019). Some of the HF patients may not have achieved the assumed ttHR during the training sessions due to the earlier achievement score of 11–12 on the Borg scale.

We divided patients into three subgroups based on the percentage of training sessions in which they achieved the assumed ttHR and compared the groups depending on the demographic and clinical characteristics. Patients enrolled in each of the subgroups achieved ttHR of more than 80%, between 20% and 80%, and in less than 20% of the training sessions, respectively.

At the end, we conducted analysis to determine whether there were differences between these groups in incidence of the secondary TELEREH-HF trial endpoints (e.g., all-cause mortality, cardiovascular mortality, cardiovascular hospitalization, HF hospitalization).

2.3 | Statistical analyses

Results for categorical variables are presented as counts and percentages and, for continuous variables, as mean and standard deviation (SD). For binary comparison, chi-square test of independence or Fisher's exact test (if the number of events in cells was less than 5) was used. Cochran–Mantel–Haenszel Modified Ridit Scores using the Row Mean Score p-value were applied for non-time-to-event ordinal variables. Continuous variables were dichotomized according to generally accepted values or the worst tertile versus other two tertiles. Events (all-cause mortality, all-cause hospitalization, cardiovascular mortality, and cardiovascular hospitalization) rates were estimated with Kaplan–Meier curves and compared by log-rank test for multiple comparisons. A two-sided p-value less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

The baseline clinical characteristics of patients are shown in Table 1. Of the 425 patients randomized to the HCTR group, 27 patients did not undergo telerehabilitation, while 12 discontinued. Ten patients discontinued telerehabilitation for non-medical reasons and two patients died for reasons not related to training sessions (1 of

TABLE 1 Baseline characteristics of the study population

Characteristic	HCTR program (n = 386)
Males, n (%)	346 (89.6)
Age, years (SD)	62 (11.0)
BMI, kg/m² (SD)	28.8 (5.1)
Left ventricular ejection fraction, % (SD)	31.0 (7.0)
Permanent atrial fibrillation or atrial flutter, n (%)	66 (17)
Etiology of heart failure	
Ischemic, n (%)	253 (65.5)
Non-ischemic, n (%)	133 (34.5)
Past medical history	
Coronary artery disease, n (%)	253 (65.5)
Myocardial infarction, n (%)	226 (58.5)
Angioplasty, n (%)	184 (47.7)
Coronary artery bypass grafting, n (%)	58 (15.0)
Hypertension, n (%)	228 (59.1)
Stroke, n (%)	21 (5.4)
Diabetes mellitus, n (%)	129 (33.4)
Chronic kidney disease, n (%)	70 (18.1)
Hyperlipidemia, n (%)	192 (49.7)
Depression BDI II >13, n (%)	75 (23.0)
Functional status (NYHA class), n (%)	
I, n (%)	51 (13.2)
II, n (%)	272 (70.5)
III, n (%)	63 (16.3)
Treatment	
Beta-blocker, n (%)	370 (95.8)
ACEI/ARB, n (%)	360 (93.3)
Digoxin, n (%)	48 (12.4)
Amiodarone, n (%)	70 (18.1)
Sotalol, n (%)	5 (1.3)
Propafenone, n (%)	1 (0.3)
Loop diuretics, n (%)	283 (73.3)
Spironolactone/eplerenone, n (%)	320 (82.9)
Aspirin/clopidogrel, n (%)	219 (56.7)
Anticoagulants, n (%)	114 (29.5)
NOAC, n (%)	62 (16.1)
Statins, n (%)	316 (81.9)
CIEDs, n (%)	305 (79.0)
CRT-D, n (%)	109 (35.7)
CRT-P, n (%)	4 (1.3)
ICD, n (%)	189 (62.0)
PM, n (%)	3 (1.0)

Abbreviations: ACE-Inhibitors, angiotensin-converting enzyme-inhibitors; ARBs, angiotensin II receptor blockers; BDI, the Beck depression inventory; BMI, body mass index; CIED, cardiovascular implantable electronic device; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy with peacemaker function; HCTR, hybrid comprehensive telerehabilitation; ICD, implantable cardioverter-defibrillator; NOAC, novel oral anticoagulants; NYHA, New York Heart Association; PM, pacemaker; SD, standard deviation.

noncardiovascular cause and 1 because of a hemorrhagic stroke) (Piotrowicz et al., 2020).

This subanalysis focuses on 386 patients (aged 62 ± 11 years, LVEF 31 ± 7%) from HCTR group who completed the 9-week telerehabilitation program. All ECGs recorded during the training sessions originated from the automatic recordings coordinated with the HCTR procedure. The most of the ECGs were of good quality, with only 3,784 (5.7%) of all 66,488 ECG recordings with artifacts.

The artifacts due to transmission failure or other technical difficulties made it impossible to assess these ECG. In 16,622 training sessions recorded, 66,488 ECGs were transmitted and evaluated.

At enrollment sinus rhythm was present in 320 (83%) and permanent atrial fibrillation (AF) in 66 (17%) patients, respectively. In 16,622 training sessions recorded, 66,488 ECGs were transmitted and evaluated. The frequency of arrhythmias at rest and during telerehabilitation training sessions is presented in Table 2. The most common arrhythmias were ventricular (VPB) and atrial (APB) premature beats, recorded in 76.4% and 27.7% of the patients, respectively. These arrhythmias did not result in any changes in rehabilitation and therapy regimens.

Resting ECG, prior to start of exercise, showed sinus rhythm without any arrhythmias in 126 (32.6%) patients, AF in 70 (18.1%) patients (in 66 [17%] as permanent and in four patients as a paroxysmal), VPB in 112 (29%) patients, NSVT in 3 (0.8%) patients, and APB in 37 (9.6%) patients (Table 2). Compared to the resting arrhythmia, the VPB, NSVT, and APB on exercise were reported in about twice as many patients, 247 (64%), 5 (1.3%), and 69 (17.9%), respectively.

There were 6 episodes of paroxysmal atrial fibrillation (AF) in 4 patients at rest who had episodes of paroxysmal AF described in their medical history. Because 3 of the 4 patients were asymptomatic, with adequate ventricular rate response and with optimal anticoagulation control, they received consent for the training sessions from supervising cardiologist. The last of the previously mentioned 4 patients had a mildly symptomatic AF during three consecutive days. This led to the temporary suspension of the training program. After treatment modification, when sinus rhythm was restored the patient continued the exercise training program.

Non-sustained ventricular tachycardia (NSVT) episodes were found only in 21 (0.03%) ECGs in 8 (2.1%) patients, and three of the episodes were recorded at rest. Episodes of NSVT consisted predominantly of 3 beats and in two cases with 4 and 5 beats, respectively. None of the patients experienced them as a symptomatic arrhythmia that could have resulted in training discontinuation. Neither death nor other serious events occurred during the telemonitored exercise training session nor directly afterward (up to 1 h) (Piotrowicz et al., 2020).

Also, as mentioned above, among 386 there were 126 patients (32.7%) without arrhythmias recorded at rest: 57 (14.8%) were also without arrhythmia on exercise, while the remaining 69 (17.9%) were with newly appearing arrhythmias on exercise. Comparison of these 2 groups depending on 9 demographic and clinical characteristics did not show significant differences between them (Table 3).

Regarding achieved ttHR during training sessions, 152 (39.4%), 130 (33.7%), and 104 (26.9%) patients achieved ttHR of more than

TABLE 2 Frequency of arrhythmias during telerehabilitation in heart failure patients (total, at rest, and on exercise)

Arrhythmia	Patient, No (%) Value (n = 386)			Number of ECG, No. (%) Value (n = 66,488)			Number of Arrhythmias, No. (%), Value (n = 11,037)		
	total	at rest	on exercise	total	at rest	on exercise	total	at rest	on exercise
Atrial premature beats	107 (27.7)	37 (9.6)	69 (17.9)	1272 (1.9)	356 (0.5)	916 (1.4)	1646 (14.9)	619 (5.6)	1027 (9.3)
Supraventricular tachycardia	2 (0.5)	1 (0.25)	2 (0.5)	6 (0.009)	2 (0.003)	4 (0.006)	6 (0.06)	2 (0.02)	4 (0.04)
Paroxysmal atrial fibrillation	4 (1.0)	4 (1.0)	0 (0.0)	6 (0.009)	6 (0.009)	0 (0.0)	6 (0.1)	6 (0.1)	0 (0.0)
Ventricular premature beats	295 (76.4)	112 (29)	247 (64)	6797 (10.2)	2372 (3.6)	4425 (6.6)	8958 (81.1)	2992 (27.1)	5966 (54.0)
Ventricular couplets	90 (23.3)	31 (8)	73 (18.9)	395 (0.6)	107 (0.2)	288 (0.4)	400 (3.6)	112 (1.0)	288 (2.6)
Non-sustained ventricular tachycardia	8 (2.1)	3 (0.8)	5 (1.3)	21 (0.03)	3 (0.04)	18 (0.026)	21 (0.2)	3 (0.04)	18 (0.16)

80%, between 20% and 80%, and in less than 20% of the training sessions, respectively.

The univariable analysis that took into account 9 demographic and clinical factors revealed that patients with atrial fibrillation or NYHA class III were significantly more frequent in groups achieved ttHR of more than 80% and achieved ttHR between 20% and 80% versus group achieved less than 20% of the training sessions (21.6% vs. 9.6%, $p = 0.007$; 19.5% vs. 8.6%; $p = 0.011$, respectively) (Table 4). There were no statistically significant differences between groups in remaining demographic and clinical characteristics. Achievement of ttHR in above 80% of training sessions compared with remaining groups did not reduce the incidence of outcomes (e.g., all-cause mortality, cardiovascular mortality, all-cause hospitalization, cardiovascular hospitalization) (Figures 1, 2, 3, 4).

4 | DISCUSSION

The main novel findings of the current study can be summarized as follows: (1) Clinically significant arrhythmias such as NSVT and paroxysmal AF episodes were very infrequently recorded during HCTR; (2) only one case of mildly symptomatic paroxysmal AF episode led to the temporary suspension of the training program; (3) most patients had benign arrhythmias (VPBs or APBs) at rest and small proportion of patients had new onset of arrhythmias on exercise; none of the clinical factors was useful in predicting new onset of arrhythmias on exercise; (4) AF and NYHA class III were identifying patients who achieved more than 80% of training sessions with ttHR reached; and (5) there was no association between achieved ttHR and outcome (all-cause mortality, cardiovascular mortality, all-cause hospitalization, cardiovascular hospitalization) in 2-year follow-up.

4.1 | Role of ECG monitoring in HF patient's telecare

ECG monitoring appears to be the crucial element for the HF patients telecare and telerehabilitation as well. Resting ECG data transmitted to the monitoring center was pivotal element of the consent for training in HCTR procedure (Piotrowicz et al., 2019). Telecare in HF patients can be defined as the monitoring of the transfer of symptoms, signs, and physiological data from a remote location to another location for the subsequent data interpretation and decision making (Piotrowicz et al., 2016). Identification of cardiac rhythm disorders, particularly clinically silent arrhythmias (such as AF and premature ventricular complexes) via ECG monitoring is important for the prevention of potential complications in the HF patients (Martirosyan et al., 2017). Besides these, increases in heart rate and ventricular arrhythmias were identified as predictors for decompensation events (Masarone et al., 2018). Early diagnosis and management of AF may prevent AF-associated complications and worsening of the HF disease course (Martirosyan et al., 2017). Cleland et al. demonstrated that ECG data transmission was significantly associated with

No arrhythmia at rest n = 126	No arrhythmia on exercise 57 (45.2)	Newly appearing arrhythmias on exercise 69 (54.8)	p-Value
Gender			
Male	47 (82.5)	59 (85.5)	0.641
Female	10 (17.5)	10 (14.5)	
Age			
≤65 years	36 (63.2)	46 (66.7)	0.681
>65 years	21 (36.8)	23 (33.3)	
Basic cardiac rhythm			
Sinus rhythm	50 (87.7)	61 (88.4)	0.906
Atrial fibrillation	7 (12.3)	8 (11.6)	
HF etiology			
Ischemic	37 (64.9)	46 (66.7)	0.836
Non-ischemic	20 (35.1)	23 (33.3)	
NYHA class			
I/II	49 (86.0)	62 (89.9)	0.502
III	8 (14.0)	7 (10.1)	
NT-proBNP (tercile)			
1 + 2	45 (78.9)	49 (71.0)	0.309
3	12 (21.0)	20 (29.0)	
LVEF (%)			
≤35	31 (54.4)	37 (53.6)	0.932
>35	26 (45.6)	32 (46.4)	
Delta pVO2 (mlO$_2$/kg/min)			
<2.0	33 (57,9)	38 (55,1)	0,751
≥2.0	24 (42,1)	31 (44,9)	
Diabetes mellitus			
Yes	20 (35.1)	20 (29.0)	0.464
No	37 (64.9)	49 (71.0)	

TABLE 3 Newly appearing arrhythmias on exercise. Comparison of no arrhythmias at rest and no on exercise group and no arrhythmias at rest and newly appearing on exercise group depending on the demographic and clinical characteristics, univariable analysis

Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNT, N-terminal fragments of B-type natriuretic peptide; NYHA, New York Heart Association.

reduced hospitalization due to HF when compared with standard care (Cleland et al., 2005). Villani et al. conducted a trial of telemonitoring and telecare for patients with chronic HF that were discharged from the hospital after being treated for clinical instability (Villani et al., 2014). They concluded that in HF patients with a high risk of relapse, the regular acquisition of simple clinical information and the access to the ECG data, produced a better psychological status and quality of life, with a reduction in hospitalizations. A meta-analysis carried out by Kotb et al. showed that telemedicine interventions, which involved the use of ECG data transmission, were significantly more effective in reducing hospitalizations due to HF when compared with standard care (Kotb et al., 2015). In the TIM-HF2 (Telemedical Interventional Management in Heart Failure II) clinical trial, it was found that remote telemonitoring including home assessment of ECG, weight, blood pressure, and general health status in the context of a 24/7 support system reduced the number of days lost due to unplanned cardiovascular (mainly HF) hospitalizations or death (Koehler et al., 2018). This study also documented a reduction in all-cause mortality for patients managed with telemedicine (Koehler et al., 2018). Seferovic et al. in a clinical practice update on HF recommended that home telemonitoring with a similar approach to the one used in TIM-HF2 may be considered for patients with HF in order to reduce the risk for recurrent cardiovascular and HF hospitalizations and cardiovascular death (Seferovic et al., 2019). They also suggested that the TIM-HF2 intervention protocol should be tested in other countries and different healthcare systems (Seferovic et al., 2019). A recent network meta-analysis of randomized controlled trials by Zhu et al. confirmed that compared to conventional healthcare, telemedicine interventions including ECG monitoring appears to be beneficial for patients with HF, particularly in reducing all-cause hospitalization, cardiac hospitalization, all-cause mortality, cardiac mortality, and the HF-related length of hospital stay (Zhu et al., 2020).

TABLE 4 Achieving target training heart rate (ttHR) during training sessions. Comparison of groups of the patients with varying degrees of achieving the training heart rate depending on the demographic and clinical characteristics, univariable analysis

	The percentage of training sessions with the ttHR reached			
	>80% N = 152 (39.4%)	20–80% N = 130 (33.7%)	<20% 104 (26.9%)	*p*-Value
Gender				
Male	138 (90.8)	116 (89.2)	91 (87.5)	0.401
Female	14 (9.2)	14 (10.8)	13 (12.5)	
Age				
≤65 years	90 (59.2)	84 (64.6)	56 (53.8)	0.487
>65 years	62 (40.8)	46 (35.4)	48 (46.1)	
Basic cardiac rhythm				
Sinus rhythm	116 (76.3)	105 (80.8)	94 (90.4)	**0.005**
Atrial fibrillation	36 (23.7)	25 (19.2)	10 (9.6)	
Sinus rhythm	221 (78.4)	94 (90.4)	**0.007**	
Atrial fibrillation	61 (21.6)	10 (9.6)		
HF etiology				
Ischemic	105 (69.1)	84 (64.6)	65 (62.5)	0.263
Non-ischemic	47 (30.9)	46 (35.4)	39 (37.5)	
NYHA class				
I/II	119 (78.3)	108 (83.1)	95 (91.3)	**0.006**
III	33 (21.7)	22 (16.9)	9 (8.6)	
I/II	227 (80.5)	95 (91.3)	**0.011**	
III	55 (19.5)	9 (8.6)		
NT-proBNP (tercile)				
1 + 2	101 (66.5)	87 (66.9)	70 (67.3)	0.884
3	51 (33.5)	43 (33.1)	34 (32.7)	
LVEF (%)				
≤35	106 (69.7)	84 (64.6)	61 (58.6)	0.068
>35	46 (30.3)	46 (35.4)	43 (41.3)	
Delta pVO2 (mlO$_2$/kg/min)				
<2.0	93 (61.2)	79 (62.7)	73 (70.9)	0.128
≥2.0	59 (38.8)	47 (37.3)	30 (29.1)	
Diabetes mellitus				
Yes	58 (38.2)	37 (28.5)	38 (36.5)	0.646
No	94 (61.8)	93 (71.5)	66 (63.5)	

Note: >80% N - number of patients who achieved target training heart rate of more than 80% of thetraning sessions. 20-80% N - number of patients who achieved target training heart rate between 20% and 80% of thetraining sessions. <20% N - number of patients who achieved target training heart rate less than 20% of thetraining sessions.

Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNT, N-terminal fragments of B-type natriuretic peptide; NYHA, New York Heart Association; ttHR, target training heart rate.

4.2 | Importance of ECG monitoring during cardiac telerehabilitation in HF patients

Piepoli et al. concluded that exercise training is recommended for stable NYHA class I–III HF patients (Piepoli et al., 2011). Supervision is mandatory during the initial phase of training program in HF patients. Continuous or frequent clinical monitoring (with the use of ECG monitoring) is also fundamental, particularly during the home training phase (Fletcher et al., 2013; Piepoli et al., 2011). To date, only one single-center study assessed ECG recordings in detail in HF patients during home-based telemonitored cardiac rehabilitation. Piotrowicz et al. evaluated 11,534 ECG fragments recorded during telerehabilitation sessions in 75 stable HF patients with reduced LVEF (30.2 ± 8.2%) (Piotrowicz et al., 2012). These results do not differ from the results of this current subanalysis. The majority of the observed arrhythmias were single VPB and APB.
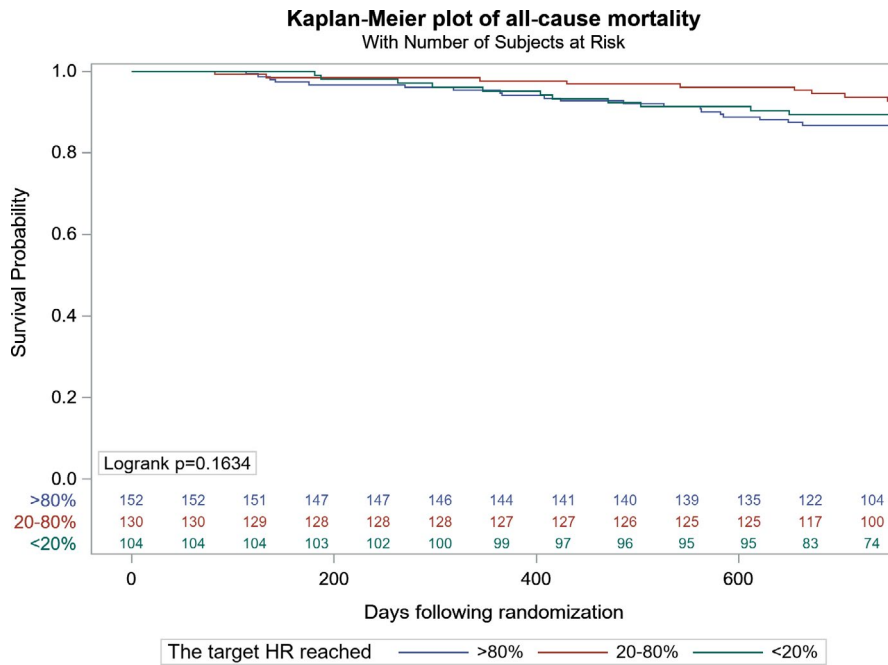
Kaplan-Meier plot of all-cause mortality
With Number of Subjects at Risk

| The target HR reached | >80% | 20-80% | <20% |

FIGURE 1 Kaplan–Meier plot of all-cause mortality-free survivals in subgroups achieved target training heart rate (HR) of more than 80% versus between 20% and 80% versus less than 20% of the training sessions
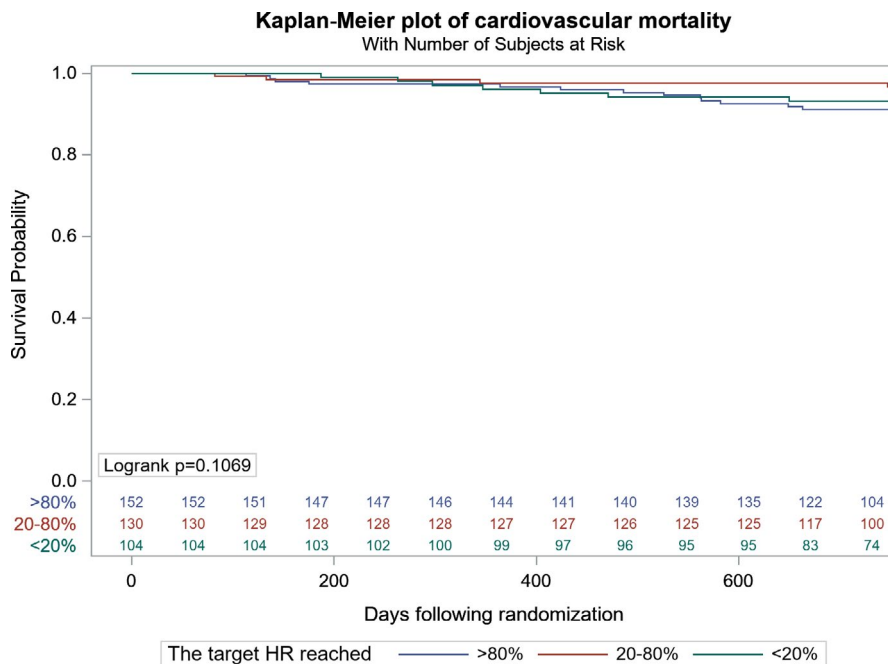
Kaplan-Meier plot of cardiovascular mortality
With Number of Subjects at Risk

| The target HR reached | >80% | 20-80% | <20% |

FIGURE 2 Kaplan–Meier plot of cardiovascular mortality-free survival in subgroups achieved target training heart rate (HR) of more than 80% versus between 20% and 80% versus less than 20% of the training sessions

The percentage of the patients who developed these arrhythmias was similar in both studies (69.3% vs. 76.4% of patients with VPB and 16% vs. 27.7% with APB). The incidence of AF was also similar (1.3% vs. 1%). This study demonstrates that in stable patients with guideline-based therapy, exercise training did not trigger significant arrhythmia requiring a change to the training workload (Piotrowicz et al., 2012). There are a few studies that investigated the cardiac telerehabilitation with ECG assessment during remote supervised exercise training sessions. Squires et al. studied transtelephonic ECG monitoring of cardiac rehabilitation in patients with coronary artery disease (Squires et al., 1991). Thirty-six of the 66 subjects enrolled to the study were classified as high-risk patients (due to LVEF <40%, history of significant ventricular arrhythmia). No serious medical emergencies occurred during the monitored exercise sessions. The authors did however discover new arrhythmia in four cases. Giallauria et al. evaluated 15 HF patients (LVEF 31 ± 9%) in home-based cardiac rehabilitation with telecardiology monitoring (Giallauria et al., 2006). They did not report any major adverse event during training sessions. In two subsequent single-center studies, no episodes of exercise-induced malignant arrhythmia were recorded (Piotrowicz et al., 2010, 2015).

The current TELEREH-HF subanalysis is the largest trial to date, which demonstrated that well-qualified, stable HF patients who underwent optimal "tailored" HCTR were not at risk in more than 16,000 training sessions. Additionally, our trial provides new insights on the sequential ECG monitoring during the home-based

FIGURE 3 Kaplan–Meier plot of all-cause hospitalization in subgroups achieved target training heart rate (HR) of more than 80% versus between 20% and 80% versus less than 20% of the training sessions
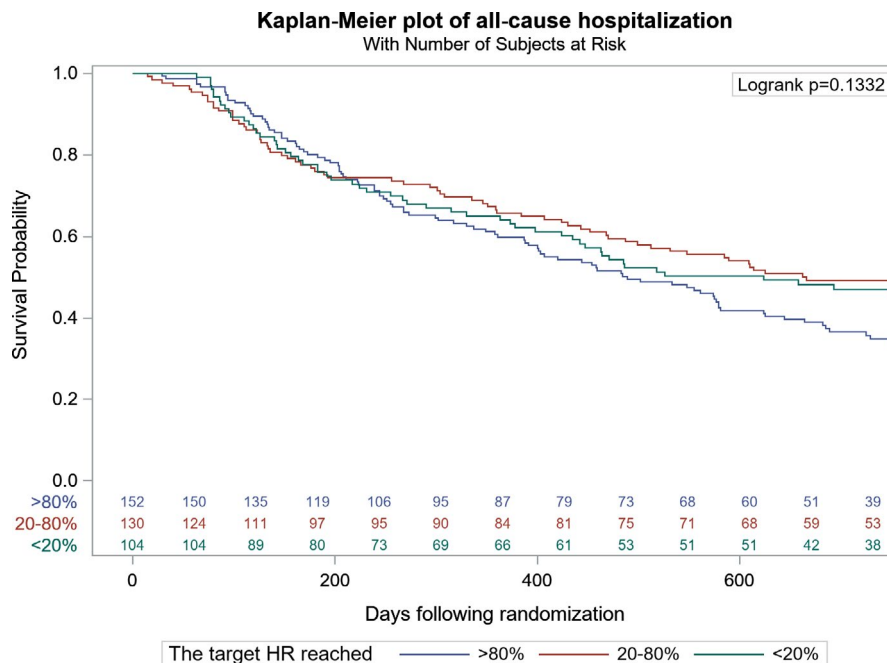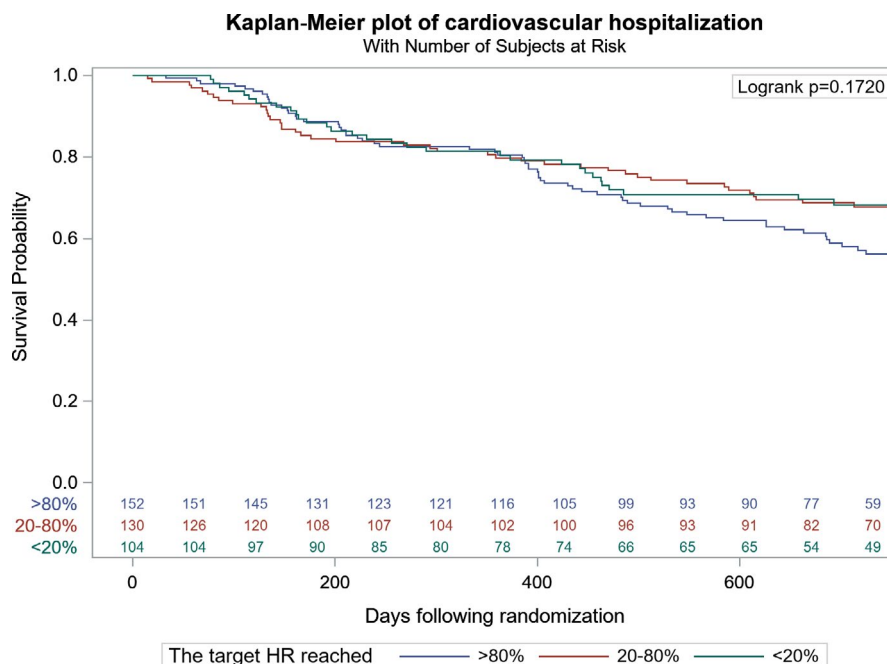
Kaplan-Meier plot of all-cause hospitalization
With Number of Subjects at Risk

Logrank p=0.1332

>80%	152	150	135	119	106	95	87	79	73	68	60	51	39
20-80%	130	124	111	97	95	90	84	81	75	71	68	59	53
<20%	104	104	89	80	73	69	66	61	53	51	51	42	38

The target HR reached — >80% — 20-80% — <20%

FIGURE 4 Kaplan–Meier plot of cardiovascular hospitalization in subgroups achieved target training heart rate (HR) of more than 80% versus between 20% and 80% versus less than 20% of the training sessions

Kaplan-Meier plot of cardiovascular hospitalization
With Number of Subjects at Risk

Logrank p=0.1720

>80%	152	151	145	131	123	121	116	105	99	93	90	77	59
20-80%	130	126	120	108	107	104	102	100	96	93	91	82	70
<20%	104	104	97	90	85	80	78	74	66	65	65	54	49

The target HR reached — >80% — 20-80% — <20%

telerehabilitation sessions in HF patients, which turned out to be a sufficient and safety form of the procedure.

Limited data exist on risk factors associated with cardiac arrhythmias during cardiac rehabilitation, especially in HF patients: Galante et al. identified diabetes and age over 70 as independent predictors associated with an increased risk in cardiac rehabilitation after coronary artery bypass surgery (Galante et al., 2000). In the present study, none of the analyzed factors increased risk of arrhythmia in context of determining onset of the newly arrhythmias on exercise.

In our population, atrial fibrillation and NYHA class III identified patients who achieved above 80% of training sessions with ttHR reached. These findings are probably associated with excessive activation of sympathetic nervous system (including heart rate

acceleration) in HF patients, which increases with decreasing the NYHA functional class (Borovac et al., 2020). Furthermore, worse heart rate control on exertion among patients with atrial fibrillation was reported (Hilliard et al., 2008). Our data also indicate that achievement of ttHR in above 80% of training sessions was not a predictor of reducing the incidence of the outcomes (e.g., all-cause mortality, cardiovascular mortality, cardiovascular hospitalization, HF hospitalization) in 2-year follow-up. In the studies on cardiac rehabilitation published so far, investigators have not analyzed the impact of the degree of ttHR achievement during training sessions on prognosis of HF patients.

In the main analysis of TELEREH-HF trail, researchers also did not find any other factor such as age, gender, Δ pVO$_2$, and HYHA

functional class that would have a positive impact on the outcomes (Piotrowicz et al., 2020).

4.3 | Limitations

It is possible that real-time continuous ECG monitoring would provide better insight, although its practical application would be difficult to implement on large scale. The forms of ECG telemonitoring (real-time vs. sequential monitoring) are still under research. In this study, only 10.5% of the participants in HCTR group were women, and therefore, care needs to be exercised when extrapolating the results for the female patient population.

5 | CONCLUSIONS

The most common arrhythmias during exercise training sessions in HF patients were ventricular and atrial premature beats. These arrhythmias did not result in any changes in rehabilitation and therapy regimen. Non-sustained ventricular tachycardia and paroxysmal atrial fibrillation episodes were rare and in only one case of mildly symptomatic paroxysmal AF episode required the temporary suspension of the training program. The model of cardiac telerehabilitation in HF patients implemented in TELEREH-HF trial was safe without evidence for symptomatic cardiac arrhythmias requiring discontinuation of telerehabilitation. Sequential monitoring of ECG should be treated as sufficient to ensure the safety of the model of cardiac telerehabilitation in HF patients implemented in TELEREH-HF trial.

ETHICAL APPROVAL
This study complied with the Declaration of Helsinki and the trial was approved by the local ethics committee (Local Bioethical Commission at the National Institute of Cardiology, Warsaw, Poland).

AUTHOR CONTRIBUTION
Piotr Orzechowski contributed to conception/design of this subanalysis, interpretation of data, and drafting of the manuscript; Ryszard Piotrowicz, Ewa Piotrowicz, and Wojciech Zaręba contributed to conception/design of this subanalysis, interpretation of data, drafting of the manuscript, critical review, and supervision; Renata Główczyńska, Dominika Szalewska, Sławomir Pluta, and Robert Irzmański contributed to acquisition of data; Maciej Banach, Grzegorz Opolski, and Zbigniew Kalarus contributed to supervision; Ilona Kowalik and Michael J. Pencina contributed to statistical analysis.

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