Impact of remote monitoring in heart failure patients with cardiac implantable electronic devices

Phd Dissertation

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List of abbreviations

AF: atrial fibrillation
ACE: angiotensin converting enzyme
ARB: angiotensin receptor blocker
ARNI: angiotensin receptor blocker/nephrilisin inhibitor
BB – β receptor blocker
COVID-19: coronavirus disease 2019
CFG: conventionally followed group
CFU: conventional follow-up
CKD: chronic kidney disease
COPD: chronic obstructive pulmonary disease
CRT-P/D: cardiac resynchronization therapy pacemaker/defibrillator
CIED: cardiac implantable electronic device
CV: cardiovascular
ESC: European Society of Cardiology
GFR: glomerular filtration ratio
HF: heart failure
ICD: implantable cardioverter defibrillator
IPE: in-office patient evaluation
LBBB: left bundle branch block
LVEDD: left ventricular end-diastolic diameter
LVESD: left ventricular end-systolic diameter
LVEF: left ventricular ejection fraction
MRA: mineralocorticoid receptor antagonist
NT pro-BNP: N terminal pro-brain natriuretic peptide
NYHA: New York Heart Association functional class
RM: remote monitoring
RMG: remote monitoring group
RPM: remote patient management
Sars Cov-2: severe acute respiratory syndrome coronavirus type 2
WHF: worsening of heart failure

I. Introduction

Relevance of heart failure patient monitoring

Heart failure (HF) is an evolving public health issue in Europe and in the United States. Despite pharmacological and non-pharmacological therapeutic advances, the rates of hospital admissions for HF means high burden for healthcare providers. Further on; a significant proportion of HF patients are readmitted to the hospital after institutional discharge in the following months. The number of hospitalizations and readmissions are constantly increasing and is responsible for a significant financial and economical burden in the western healthcare systems.

Patients are usually admitted to the hospital because of worsening heart failure symptoms, such as significant decrease in functional capacity, signs and symptoms of congestion or low-cardiac output syndrome. Symptoms of cardiac decompensation are often associated with increased filling pressures of atrias and ventricles of the heart which result in pulmonary and/or systemic signs and symptoms of congestion. Changes in intracardiac hemodynamics are usually apparent several weeks before hospital admission, thus certain monitoring devices have the ability to preemptively warn for worsening cardiac condition and for a potential cardiac decompensation event (**Figure 1.**). Such early detection and preemptive adequate pharmacological/ non-pharmacological interventions may have the potential to effectively prevent worsening heart failure patients from hospitalization.
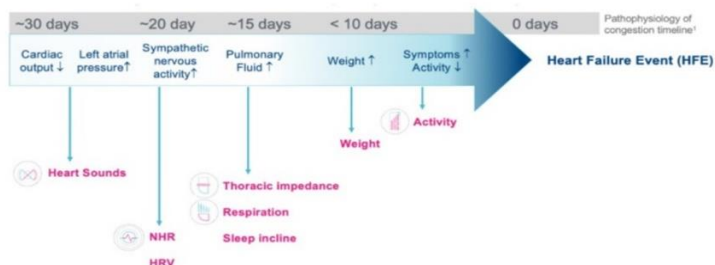

Figure 1. Evolving changes in cardiac physiology and hemodynamics during worsening of heart failure. Pathophysiological changes of certain physiological parameters may preemptively warn for an upcoming cardiac decompensation event even weeks before apparent signs and symptoms of circulatory congestion.
Source: www.bostonscientific.com/electoroppysiology/heartlogic

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In the early 2000s, remote monitoring of implantable cardiac defibrillators was introduced. This technology allows continuous monitoring of device integrity (pacing thresholds, sensing function, electrode impedance, shock impedance) and several physiological parameters (resting heart rate, heart rate variability, patient activity, arrhythmia events) related to the exacerbation of HF as well.
Further step in patient-device remote monitoring was made by the installation of algorithms measuring the patient's intrathoracic impedance. Monitoring of these parameters have role in the predilection and early detection of worsening heart failure.

Remote monitoring systems

Most of the contemporary available ICD and CRT systems are capable of wireless data transmission. Measurable transmittable parameters are depending of the device manufacturers and are usually transmitted to a data repository in predefined (days, weeks) time intervals using either analog or digital landlines or nowadays more preferably wireless data networks. Remote monitoring of devices provides continuous surveillance of device integrity and shows whether clinically relevant event for the patient occurred. In case of device integrity problems or significant alterations in the patient's physiological parameters, arrhythmias the system sends warning signs to the healthcare provider staff through an available online software system and the patient may get 'flagged' for attention. Thresholds for warning are often preprogrammed, but certain device manufacturers allow programmable warning-sign thresholds.

Alert events given by remote monitoring system can be in connection of relevant clinical (atrial fibrillation burden, ventricular arrhythmias, ventricular shock event) or of technical nature (abnormal electrode impedance, elevated threshold in a paced chamber, signal sensing, low biventricular pacing ratio).
Randomized controlled trials found remote interrogation safe and effective method of patient surveillance compared to in-office patient evaluation (IPE) based follow-up. **Table 1**. summarizes characteristics of different remote monitoring systems according to manufacturers.
Cybersecurity is ensured by all device manufacturers regarding data transfer to the server and the hospital.

Manufacturer	Biotronik	Medtronic	Boston Scientific	St Jude Medical	LivaNova
Name	Home Monitoring™	Carelink™	Latitude NXT™	Merlin.net™	SMARTVIEW™
Telecommunication network	GPRS/3G	GPRS/3G, analogous phone line	3G, analogous phone line	3G, analogous phone line	GPRS, analogous phone line
Internet based availability	-	+	+	+	-
Remote monitoring	+	+	+	+	+
Remote follow-up	+	+	+	+	+
Direct data transmission	+	+	-	-	-
Patient triggered data transmission	-	+	+	+	+
Transmitter unit	mobile	stationary	stationary	stationary	stationary
Time interval of scheduled data transmission	daily	1 week – 1 year	1 week – 1 year	1 week- 1 year	1 day – 1 year
Real Time IEGM sample per data transmission	1	All recorded	All recorded	All recorded	Maximum 3 samples
Programmability of warning sign thresholds	+	+	+	+	-
Special attribute	Thoracic impedance monitoring	Thoracic impedance monitoring (OptiVol™)	Bodyweight and blood pressure monitoring	Thoracic impedance monitoring (CorVue™)	

Table 1. Comparison of different remote monitoring systems. Based on the work of Prof. Dr. Zima E. et al.
GPRS: General Pocket Radio Service, 3G: third generation internet network, IEGM: intracardiac electrocardiogram.

Multiparametric monitoring of CIEDs

Continuous multiparametric monitoring HF patients living with CIEDs can improve the prognosis and clinical outcomes by identifying certain patients having higher risk for an upcoming decompensation event. The identification of several parameters and multiparametric scores are able to predict worsening of heart failure (WHF), and may improve identification and facilitate better management strategies for patients at risk of HF events. PARTNERS-HF study (The Program to Access and Review Trending Information and Evaluate Correlation to Symptoms in Patients with Heart Failure) was designed to determine the potential utility of multiple device diagnostic parameters in predicting HF events and potential hospitalization.

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The device diagnostic parameters included thoracic impedance, atrial fibrillation burden, ventricular rate during atrial fibrillation, sustained ventricular arrhythmia episodes, patient activity, resting heart rate and heart rate variability. An algorithm combining changes in these device diagnostic parameters improved the ability to identify patients at risk of decompensated HF event in the next 30 days. Based on the upper parameters a HF device diagnostic criterion algorithm was introduced, which had the ability to classify the patient's risk for HF hospitalization in the next 30 days as high, medium and low. PARTNERS-HF study also showed that OptiVol™ based thoracic impedance alert positivity alone had only a 2.7 hazard ratio whereas combined device diagnostic multiparametric alert positivity produced a 5.5 hazard ratio for an upcoming HF event.

In Hungary, Vámos M. et al. were utilizing a HF prediction algorithm based on the parameters used in PARTNERS-HF study. Vámos et al. refined the detection criteria for worsening HF event in a multi-center prospective validation study. The refined algorithm was shown to have an 86% sensitivity and 93% specificity for an upcoming HF event in a previously CRT implanted patient group.

There is a persisting need for a sophisticated and universally accepted automatic data transmission-based monitoring system for predicting heart failure deterioration in CIED patients.

Name of Randomized Trial	Follow-up time (months)	Population size	Age (years)	Male gender (%)	LVEF (%)	ICM (%)	NYHA III-IV (%)	Monitored parameter(s)
TRUST [17]	12	1339	64	73	29	67	30	VT, VF, ineffective ventricular shock, atrial mode switch >10%/24h
CONNECT [18]	15	1997	65	71	29	62	50	AF burden, high ventricular rate during AF, ventricular shock count
EVOLVO [19]	16	200	67	79	31	46	19	AF burden, thoracic impedance, ventricular shock count
ECOST [20]	24	433	62	88	35	65	9	VT, VF, AF, ineffective ventricular shock, atrial mode switch >75%/18h
IN-TIME [21]	12	664	65	82	26	70	57	VT, VF, AF, biventricular pacing ratio, patient activity, PVC/h
OptiVol [22]	15	176	66	77	32	53	43	Thoracic impedance
OptiLink HF [23]	18	1002	66	80	27	54	81	Thoracic impedance
REM-HF [24]	34	1650	70	86	30	68	30	AF burden, biventricular pacing ratio, thoracic impedance, patient activity, heart rate variability, ventricular arrhythmias
MORE-CARE [25]	24	865	66	76	27	44	60	AF burden, thoracic impedance

Table 2. Randomized controlled trials of CIED implanted remote monitored heart failure patients. *AF: atrial fibrillation/flutter/tachycardia, CIED: cardiac implantable electronic device, h: hour, LVEF: left ventricular ejection fraction, ICM: ischemic cardiomyopathy, NYHA: New York Heart Association functional class, PVC: premature ventricular contraction, VT: ventricular tachycardia, VF: ventricular fibrillation*

Results of previous randomized controlled trials

Several randomized clinical trials were conducted to evaluate the overall impact of remote monitoring on clinical outcomes in patients with ICD or a CRT-D (**Table 2.**). Majority of these trails also performed telemedicine-based disease management strategy telephone interviews or even unscheduled in-office patient evaluations.
Only IN-TIME (Influence of Home Monitoring on mortality and morbidity in heart failure patients with impaired left ventricular function study) observed significant reduction in all-cause mortality with remote monitoring (RR: 0.35; 95%CI: 0.17 to 0.73; p=0.005). The most prominent result regarding mortality was seen in a non-permanent atrial fibrillation patient group (patients with paroxysmal or persistent atrial fibrillation).
Meta-analysis by Parthiban et al. examined the effect of competing remote monitoring technologies on all-cause mortality. Pooled results of three trials using remote monitoring technology from Biotronik (Berlin, German) using daily transmission technology a reduction in all-cause mortality with automatic daily remote monitoring was observed (RR: 0.65; 95% CI: 0.45 to 0.94; p=0.02). This result was supported by an independent analysis using patient data of the same three randomized controlled trials (TRUST, ECOST, IN-TIME). In this investigation the absolute risk of all-cause mortality was reduced by 1.9% with active daily data transmission based remote monitoring in ICD and CRT-D implanted HF population.

Data on HF hospitalizations were reported in four randomized controlled trials enrolling 2707 patients. The pooled data analysis of these studies showed no significant reduction in the relative risk of hospitalization due to HF.

The impact of remote monitoring in heart failure patients with atrial fibrillation should be emphasized. Atrial fibrillation (AF) can be accurately quantified by remote monitoring in most cases when an atrial electrode is implanted. AF has been linked not only increased incident of strokes and inappropriate defibrillator shocks but is also an important cause of increased risk for HF hospitalization as well. Especially patients with and implanted CRT device AF with high ventricular rate can directly reduce biventricular pacing ratio which limits the efficacy of resynchronization therapy. Therefore, early detection of AF by remote monitoring affords optimization of rate- or rhythm control strategies that may prevent AF-related HF decompensation.

An example of HF remote monitoring system published in the IN-TIME study before (Biotronik Home Monitoring™, Berlin, Germany) is shown from our patient population on **Figure 3**.

Figure 3. Biotronik Home Monitoring™ heart failure monitor.
Our CRT defibrillator implanted heart failure persistent atrial fibrillation patient's
Home Monitoring trend is shown in the Figure above. After unsuccessful
pharmacological rhythm control strategy, a successful pulmonary vein isolation
procedure was performed. After the index event the biventricular pacing ratio is
restored, the atrial- and ventricular rates and heart rate variability are normalized,
further on: atrial fibrillation burden seems to vanish, even thoracic impedance value
shows moderate increase (improvement).

**Conclusion of previous studies and future devices dedicated to HF
monitoring**

All aforementioned studies have led observers to question the usefulness of
remote monitoring in the HF setting. It should be emphasized, that these

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trials were heterogenous in methodological quality, sample size, severity of HF, monitoring data, frequency of data transmission and clinical response to alert events. Remote monitoring of device data is feasible but the impact is highly dependent on the process of clinical decision -making on the remote transmitted data.

Seeing the previous study results above, the impact of remote monitoring in heart failure CIED patients is not standing without a doubt.

There can be considerable benefits in the following clinical circumstances for remote monitoring:

- Automatic, daily data transmission based remote monitoring system
- Advanced heart failure with NYHA functional class III-IV/a
- Patients with non-permanent (paroxysmal, persistent) AF in history
- One or more HF hospitalization events in patient history
- Good patient adherence

There is lack of consensus on choosing the most appropriate, universally accepted and utilized physiologic parameters to monitor at HF patients. Alert threshold levels are still needing supporting evidence through large randomized controlled trials with considerable patient sample sizes.

II.   Focus and aim of the studies

General aspects

Effective remote patient management (RPM) via CIEDs has long been achievable but due to lack of adoption of easy manageable algorithm-driven alert-based systems and absence of randomized protocols this technology was underutilized until now.

We tested our institutional RM heart failure detection algorithm protocol **(Figure 4.)** using adapted and refined PARTNERS-HF criteria for an automated daily data transmission enabling RM system (Biotronik Home Monitoring ™). We assumed that refined RM detection criteria associated workflow and early interventions aiming at prevention of decompensated heart failure events can decrease heart failure-related hospitalizations and increase survival compared to a conventional 'ambulatory-only'- followed patient group, without increasing hospital ambulatory burden or the number of unscheduled unnecessary in-office patient evaluations in an RM-followed CRT implanted patient group.
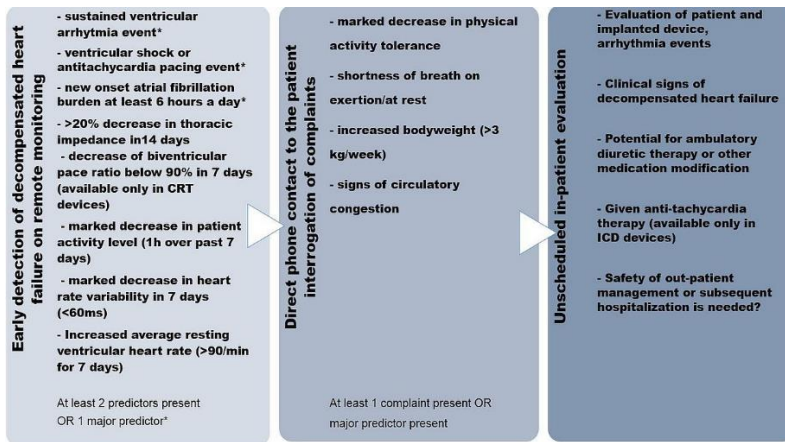
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Early detection of decompensated heart failure on remote monitoring

- sustained ventricular arrhytmia event*
- ventricular shock or antitachycardia pacing event*
- new onset atrial fibrillation burden at least 6 hours a day*
- >20% decrease in thoracic impedance in14 days
- decrease of biventricular pace ratio below 90% in 7 days (available only in CRT devices)
- marked decrease in patient activity level (1h over past 7 days)
- marked decrease in heart rate variability in 7 days (<60ms)
- Increased average resting ventricular heart rate (>90/min for 7 days)

At least 2 predictors present OR 1 major predictor*

Direct phone contact to the patient interrogation of complaints

- marked decrease in physical activity tolerance
- shortness of breath on exertion/at rest
- increased bodyweight (>3 kg/week)
- signs of circulatory congestion

At least 1 complaint present OR major predictor present

Unscheduled in-patient evaluation

- Evaluation of patient and implanted device, arrhythmia events
- Clinical signs of decompensated heart failure
- Potential for ambulatory diuretic therapy or other medication modification
- Given anti-tachycardia therapy (available only in ICD devices)
- Safety of out-patient management or subsequent hospitalization is needed?

Figure 4. Institutional algorithm and workflow for preemptive detection of HF
Major predictor positivity (*) led to a consequent unscheduled in-office patient evaluation (IPE). In case of at least 2 minor predictor positivity hospital staff contacted directly the patient interrogating HF signs and symptoms on a predefined formula. Ambulatory IPEs were categorized to clinically necessary and unnecessary visit events.

In our hypothesis; daily data transmission based remote monitoring, weekly check-up of transmitted data trends and close telephone-based follow-up scheme can improve patient's prognosis regarding HF outcomes and may have potential role in lower CV mortality. We assumed that remote monitoring can enhance ambulatory care efficacy in this patient group compared to a conventional (IPE based) standard followed patient group.

III.   Automatic daily remote monitoring in heart failure patients implanted with cardiac resynchronization therapy-defibrillator; a single center observational pilot study

Introduction

It has been shown that RM is a safe and reliable method in the follow-up of patients with advanced heart failure and implantable cardiac defibrillators (ICD). The detection times of major adverse clinical events such as arrhythmia events, silent atrial fibrillation, inappropriate ventricular shocks, and even device-related malfunction and impending heart failure events are significantly shorter than with conventional in-office follow-up. In this study, we tested our institutional RM heart failure detection algorithm protocol using adapted and refined PARTNERS-HF criteria for an automated daily transmission enabling RM system (Biotronik Home Monitoring ™).

We assumed that refined RM detection criteria and early interventions aiming at prevention of decompensated heart failure events can decrease heart failure-related hospitalizations and may increase survival compared to a conventional 'ambulatory-only'- followed patient group, without increasing hospital ambulatory burden or the number of unnecessary unscheduled in-office patient evaluations in an RM-followed patient group of CRT-D-implanted patients.

Methods

This investigation was a single-center retrospective observational pilot study involving 2 parallel cohorts consisting of heart failure patients. All patients were implanted with Biotronik Iforia™ CRT-D devices from 2014 January to 2017 December in our university referral hospital. Patients received a de novo implanted CRT-D device in accordance with the current ESC guidelines for heart failure therapy. All implanted CRT-D devices were eligible for remote monitoring. Cardiomessenger™ remote transmission devices were provided by the manufacturer, and the availability was not continuous during the implantation period.

Conventionally followed patients received an Iforia CRT-D device capable of RM function as well. Only 1 of 44 patients in the conventionally followed (CFU) group refused remote monitoring follow-up; this patient was excluded from the study. The other 43 patients in the CFU group had no possibility to receive a remote transmission device at the time of

implantation. Patients were non-randomized is this study, but it should be noted that no significant differences were observed in the most important baseline characteristics between the 2 patient groups. All patients signed a written informed consent form. All CRT-D devices and the automatic daily basis tele-monitoring system (Home Monitoring™) were provided by Biotronik (Biotronik SE & Co., KG, Berlin, Germany

Follow-up data of 88 de novo CRT-D-implanted patients were collected and analyzed. The remote monitored CRT-D-implanted patients (RM group, n = 45) were followed with automatic daily transmission-based continuous remote monitoring, and remote interrogation of the device was performed every 3 months. At least one scheduled yearly in-office follow-up visit was agreed with these patients. Alerts were received based on Home Monitoring's intrinsic alert algorithm. Remote transmissions, including alerts, were observed daily by a competent nurse staff, and all the relevant transmissions were immediately forwarded to a device/heart failure specialist. CRT-D-implanted patients with conventional follow-up (CFU group, n = 43) had a scheduled in-clinic ambulatory appointment every 3–6 months during follow-up, depending on the treating cardiologist/device specialist.

Data collection was performed in accordance with international regulations regarding the protection of personal information and data. All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the University of Pécs (6600/2020).

Novel detection algorithm for worsening heart failure in remote monitoring group

Several parameters served as additional accessible information for the heart failure status of the patient in the RM group during follow-up. The PARTNERS HF prospective multi-center observational study published a combined heart failure device algorithm for predicting an upcoming heart failure event. The algorithm consisted of long atrial fibrillation duration (> 6 hours/day for at least 1 day, without persistent AF), rapid ventricular rate (daily average above 90/min for at least 7 days), high thoracic fluid index (above 60 Ohms), low patient activity below 1 hour/ day over 7 days, high nocturnal ventricular rate (> 85/min for 7 consecutive days), low heart rate variability (< 60 ms for 7 days), low biventricular pacing ratio (< 90% for 5 of 7 days), or at least 1 ventricular shock event. The algorithm was considered positive if a patient had 2 positive criteria during a 1-month period. Vámos et al. investigated thoracic fluid index alerts in a prospective observational study and refined the PARTNERS HF algorithm to a modified version, increasing the algorithms specificity to 86.5% and sensitivity to

93.8% in predicting an upcoming heat failure event. In our study, the automated daily continuous remote monitoring method allowed assessment of patient activity level, ventricular heart rate at rest, heart rate variability, intrathoracic impedance tendency, biventricular pacing ratio, and all arrhythmia and anti-tachycardia therapy events. In the CFU group, these data were only available every 3-6 months at in-office follow-ups. **Table 3.** compares refined PARTNERS HF criteria and our institutional remote monitoring criteria for an upcoming decompensated heart failure event. In our criteria system the major predictors for a heart failure event were sustained ventricular arrhythmia, ventricular appropriate or even inappropriate shock or anti-tachycardia pacing events, and new-onset atrial fibrillation burden exceeding 6 hours for at least one day. Upon detection of even 1 major criterion, patients were called in for an unscheduled visit. Minor criteria were a decrease of thoracic impedance of at least 20% in the last 7 days, a decrease of biventricular pacing ratio below 90% in the last 7 days, a marked decrease (< 1 hour a day) of patient activity level in the last 7 days, a marked decrease in heart rate variability (< 60 ms) in a week, or an increased resting ventricular heart rate for 7 days (> 90/min). If no major but at least 2 minor RM criteria for worsening heart failure state were positive at remote interrogation, an immediate direct telephone consultation was made with the patient and even minor symptoms associated with an impending cardio-circulatory decompensation were interrogated. If the patient's symptoms were positive, an unscheduled urgent in-office visit was arranged. Unscheduled ambulatory visits had the aim for a pre-emptive medical- or device-mediated intervention, thus preventing patients from further deterioration and hospitalization for decompensated heart failure.

Device parameter	refined PARTNERS HF criteria [13]	Remote monitoring criteria for decompensated heart failure event
Thoracic fluid index alert	elevated thoracic fluid index (>60 Ohm)	>20% decrease in thoracic impedance value for 7 days
New onset AF episode	AF>6h on at least one day without persistent AF	new onset AF at least 6h a day without persistent AF
Ventricular rate during AF	AF> 24 h and daily average ventricular rate during AF >90/min	not used
Average daily ventricular heart rate	not used	>90/min for 7 consecutive days
Patient activity level	Lower average activity in the past 5 days	Lower average activity in the past 7 days
Nocturnal heart rate	Average night rate >85/min, or elevated with 20 over the past 5 days	not used
Heart rate variability	<60 ms every day for one week	<60 ms every day for one week
Biventricular pacing ratio	<90% in the past 5 days	<90% in the past 7 days
Ventricular arrhythmias	ventricular shock or anti-tachycardia pacing events	ventricular shock, anti-tachycardia pacing events or sustained ventricular arrhythmias

Table 3. Comparison of refined PARTNERS-HF (Vámos et al.) and remote monitoring criteria for predicting decompensated heart failure event in our institute.

Statistical analysis

All follow-up variables were divided to categorical or continuous variables. Data are presented as mean ± standard deviation for normally distributed continuous variables, median (25th and 75th percentiles) for non-normally distributed variables, or percentages for binary variables. Missing data were not replaced; all available data were used for sample distribution evaluation. Normality was checked with the Kolmogorov-Smirnov test. For normally distributed data Student's t-test was used. The Mann-Whitney test was used for inter-individual comparisons of continuous variables when normality was rejected. Categorical variables were compared with the chi-square or Fisher's exact test. For cardiovascular survival analysis we applied Kaplan-Meier survival curve estimation with log rank test and Cox's

regression with forward selection. Statistical analysis was performed using IBM SPSS statistical software version 25.0. (Armonk, NY, IBM Corp.). Post hoc power analysis was performed for the primary endpoint outcome based on Kaplan-Meier survival analysis using Stata version 15 (Stata Corp. 2017. Stata Statistical Software: Release 15. College, TX: Stata Corp LLC.). The level of significancy was defined as $p < 0.05$.

Results

Total of 88 CRT-D recipients were included in the study. Patient baseline characteristics are summarized in **Table 4.**

Characteristic	RM group (n=45)	CFU group (n=43)	p value
Age (years), mean (SD)	59.7 (10.6)	62.6 (10.5)	0.200
Female, n (%)	12 (26.7)	7 (16.3)	0.230
Left ventricular ejection fraction (%), mean (SD)	29.49 (5.1)	30.27 (4.4)	0.471
NYHA class, mean (SD)	2.82 (0.71)	2.88 (1.41)	0.202
II n (%)	15 (33.3)	9(20.9)	
III n (%)	23(51.1)	30(69.8)	
IV n (%)	7(15.6)	4(9.3)	
Left bundle branch block, n (%)	42 (93.3)	40 (93.0)	
Ischemic etiology, n (%)	25 (55.5)	25 (58.1)	0.860
Hypertension, n (%)	35 (77.8)	35 (81.4)	0.674
Diabetes, n (%)	17 (37.8)	13 (30.2)	0.821
Hyperlipidemia, n (%)	11 (24.4)	8 (18.6)	0.543
COPD, n (%)	6 (13.3)	8 (18.6)	0.499
Chronic kidney disease, n (%)	2 (4.4)	3 (6.9)	0.673
Atrial fibrillation, n (%)	11 (24.4)	11 (25.6)	0.900
Medications at the time of implantation			
Beta receptor blockers, n (%)	41 (91.1)	39 (90.7)	1.000
ACEi /ARB, n (%)	37 (82.2)	37 (86.0)	0.590
MRA, n (%)	31 (68.9)	24 (55.8)	0.310
Diuretics, n (%)	40 (88.9)	39 (90.7)	1.000
Amiodarone, n (%)	14 (31.1)	9 (20.9)	0.377
Anticoagulants, n (%)	20 (44.4)	26 (60.5)	0.120
Antiplatelet agent, n (%)	22 (48.9)	20 (46.5)	0.991
Statin, n (%)	27 (60.0)	13 (30.2)	**0.008**

Table 4. Comparison of baseline patient characteristics. *NYHA class: New York Heart Association class; COPD: chronic obstructive pulmonary disease; ACEi: angiotensin-converting-enzyme inhibitor; ARB: angiotensin-receptor blocker; MRA: mineralocorticoid-receptor-antagonist*

Improved cardiovascular survival and less hospitalization for heart failure in the remote monitoring group

Significantly lower CV mortality was observed (1 vs. 6; $p = 0.04$) in the RM group during follow-up (**Figure 5.**). The Kaplan-Meier estimate of 1-year CV mortality was 1.45% in the RM group and 6.92% in the CFU group.

Potential parameters for predicting CV mortality were divided into 3 parameter subgroups. Relevant patient baseline characteristics, follow-up parameters, and medication factors were analyzed for predicting CV mortality in our patient cohort. Cox-regression analysis showed that, among baseline characteristics, NYHA class (HR = 2.69; 95% CI: 0.01–7.17; $p = 0.047$) was an independent predictor. Among follow-up factors, only the occurrence of a hospitalization event for decompensated heart failure (HR = 3.24; 95% CI: 1.19–8.84; $p = 0.022$) was a significant, independent predictor for CV mortality. (**Figure 6.**). In terms of hospitalization events for decompensated heart failure we noted a significant difference, with the RM group performing better (8 vs. 29; $p = 0.046$) (**Table 5.**).
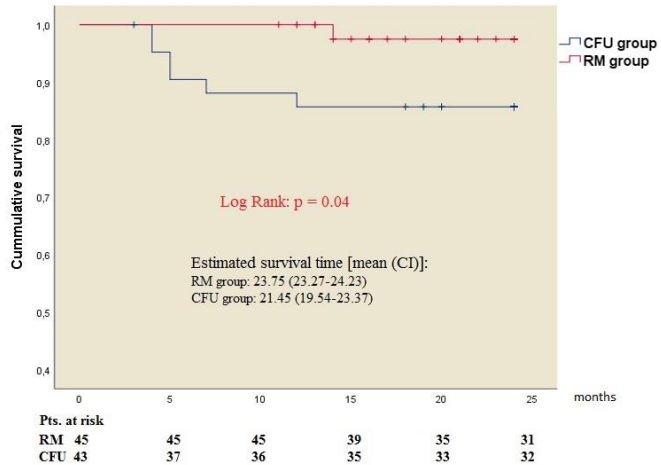
Figure 5. Kaplan-Meier's curve for estimated cardiovascular mortality in patient groups
Significantly better cardiovascular survival (1 vs. 6 cases; p = 0.04) was observed in the remote monitoring patient group after 25 months of investigation.
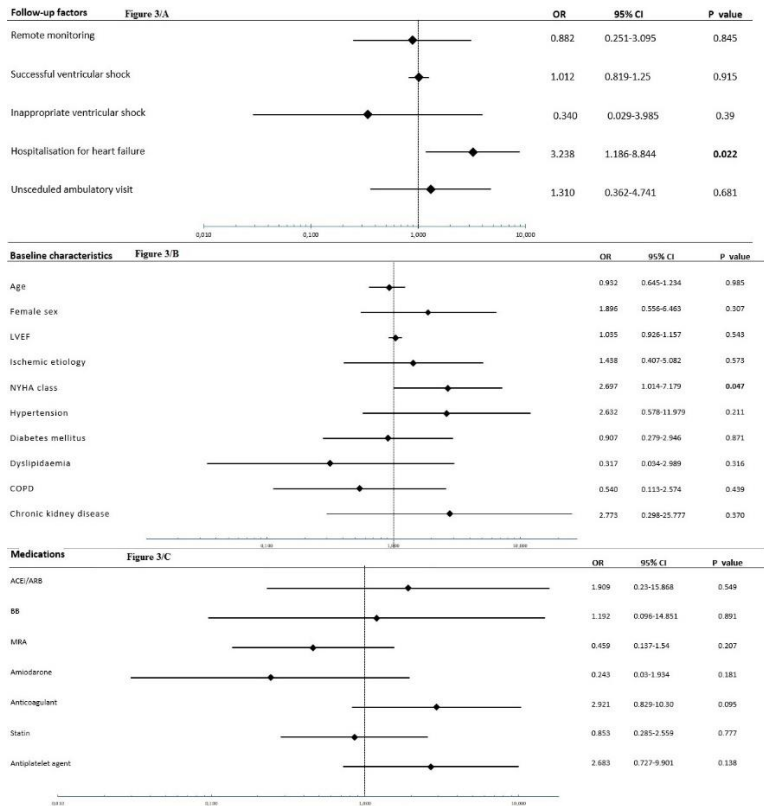*RM group – remote monitoring group, CFU group – conventional follow-up group*

Figure 3/A

Follow-up factors	OR	95% CI	P value
Remote monitoring	0.882	0.251-3.095	0.845
Successful ventricular shock	1.012	0.819-1.25	0.915
Inappropriate ventricular shock	0.340	0.029-3.985	0.39
Hospitalisation for heart failure	3.238	1.186-8.844	**0.022**
Unsceduled ambulatory visit	1.310	0.362-4.741	0.681

Figure 3/B

Baseline characteristics	OR	95% CI	P value
Age	0.932	0.645-1.234	0.985
Female sex	1.896	0.556-6.463	0.307
LVEF	1.035	0.926-1.157	0.543
Ischemic etiology	1.438	0.407-5.082	0.573
NYHA class	2.697	1.014-7.179	**0.047**
Hypertension	2.632	0.578-11.979	0.211
Diabetes mellitus	0.907	0.279-2.946	0.871
Dyslipidaemia	0.317	0.034-2.989	0.316
COPD	0.540	0.113-2.574	0.439
Chronic kidney disease	2.773	0.298-25.777	0.370

Figure 3/C

Medications	OR	95% CI	P value
ACE/ARB	1.909	0.23-15.868	0.549
BB	1.192	0.096-14.851	0.891
MRA	0.459	0.137-1.54	0.207
Amiodarone	0.243	0.03-1.934	0.181
Anticoagulant	2.921	0.829-10.30	0.095
Statin	0.853	0.285-2.559	0.777
Antiplatelet agent	2.683	0.727-9.901	0.138

Figure 6. Variable regression analysis for predictors of mortality in 3 parameter groups (follow-up parameters (A), baseline characteristics (B), medications (C)).
Analysis for cardiovascular mortality predictors was performed in 3 different parameter groups (A, B, C). New York Heart Association class (p = 0.047) and hospitalization event for decompensated heart failure (p = 0.022) were significant predictors of cardiovascular mortality in our patient cohorts.
LVEF – left ventricular ejection fraction, NYHA – New York Heart Association, COPD – chronic obstructive pulmonary disease, ACEi – angiotensin-converting-enzyme inhibitor, ARB – angiotensin-receptor-antagonist, BB –β-receptor blocker, MRA – mineralocorticoid-receptor-antagonist.

Hospitalization, arrhythmias, and defibrillator therapy
Institutional admissions for novel or high-ventricular rate atrial
fibrillation treatment, cumulative ventricular arrhythmias/ventricular
shocks, or general check-up prior to heart transplantation were
registered in both groups. We noted a trend for higher count in the RM
group in atrioventricular node ablation procedures and other device-
related operative procedures: 4 pacing electrode change/repositioning
and 4 pocket hematoma evacuations were performed in the RM group,
whereas 2 pacing electrode revision and 1 pocket hematoma
evacuation in the CFU group were performed (**Figure 7.**).

Characteristic	RM group (n=45)	CFU group (n=43)	p value
Follow-up time (months), median (IQR)	30 (20-39)	24 (16-33)	0.06
Cardiovascular mortality, n (%)	1 (2.2)	6 (13.9)	**0.04**
Cardiovascular hospitalization events, n	37	46	0.76
Days spent for cardiovascular hospitalizations, n	245	346	0.35
Hospitalization events for decompensated heart failure, n	8	29	**0.046**
Total ambulatory visits, n	161	263	**<0.01**
Unscheduled ambulatory visits, n	36	22	0.167
Unscheduled unnecessary ambulatory visits, n	6	19	**0.012**
Ventricular arrhythmias, n	243	205	0.067
Anti-tachycardia pacing events, n	114	81	0.876
Appropriate, successful ventricular shocks, n	50	44	0.23
Inappropriate ventricular shocks, n	11	13	0.83
Patients with inappropriate ventricular shocks, n (%)	4 (8.8%)	3 (6.9%)	0.74
Biventricular pace ratio (%), mean (±SD)	98.9 (8.0)	98.7 (6.6)	0.93
Control left ventricular ejection fraction (%), mean (±SD)	33.1 (9.69)	32.2 (11.1)	0.91

Table 5. Follow-up related results.

	Remote monitoring group	Conventional followed group
Hospitalisation for decompensated heart failure	8	29
Hospitalisation for atrial fibrillation event	6	7
Hospitalisation for cumulated ventricular arrhythmia / shock event	5	6
Atrioventricular node ablation procedure	3	1
CRT device related operative procedure	8	4
Management for heart transplantation	2	2

Figure 7. Distribution of cardiovascular hospitalization events during follow-up.
Higher number of hospitalizations for worsening heart failure is observable in the CFU group (8 vs. 29, p = 0.046). There were no significant differences regarding other cardiac or device-related hospitalization events.

Effectivity of institutional ambulatory care

During median 30 months of follow-up 38521 daily remote transmissions were made, and 93% of remote transmissions were successful in the RM group. Detection algorithm positivity for major/minor predictors of an upcoming decompensated heart failure event were assessed weekly with the help of competent nursing staff and an onsite device/heart failure specialist. Significant results were seen in connection with ambulatory patient flow.

	Remote monitoring group	Conventional followed group
Unscheduled unnecessary ambulatory visits	6	19
Unscheduled necessary ambulatory visits	30	3
Scheduled ambulatory visits	125	241
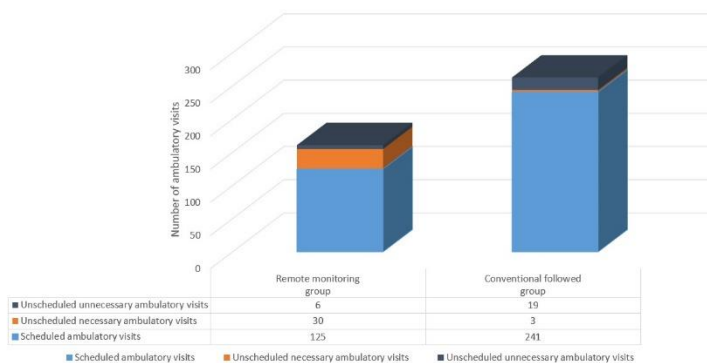
Figure 8. Ambulatory follow-up burden in the patient cohorts.
Ambulatory patient flow graph shows a total 39% (161 vs. 263) reduction of ambulatory admissions between the 2 patient groups (p < 0.01). A significantly lower (6 vs. 19; p = 0.012) number of unnecessary ambulatory patient admissions were also observed.

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Discussion

This study sought to evaluate the impact of a novel remote monitoring heart failure detection algorithm, designed for an automatic daily transmission-based remote monitoring system. Our RM detection algorithm seems to show efficacy at improving advanced heart failure patient survival, decreasing heart failure-related hospitalizations and institutional ambulatory patient burden beneath more effective in-office patient care even in our pilot study with moderate patient cohorts.

The daily data transmission-based algorithm seems important in improving patient outcomes, because tele-monitoring algorithms, typically with weekly data transmission (MORE CARE study), failed to prove the benefit of remote monitoring in heart failure patients.

None of the previously performed studies and meta-analyses reported improved cardiovascular patient survival, decreased hospitalization rate for heart failure, or decreased institutional ambulatory burden with improved efficacy of the ambulatory care in the same remote-monitored advanced heart failure CIED patient population.

We adapted modified PARTNERS HF criteria to Biotronik CRT defibrillators capable of daily remote transmission and refined the prediction criteria based on well-documented previous literature and clinical experience.

In our RM cohort, the remote monitoring follow-up method was not an independent predictor for patient cardiovascular mortality in our investigation; however, can be assumed that the lower count of hospitalization for decompensated heart failure observed in the RM group may directly and independently play an important role in lower cardiovascular mortality compared to conventionally followed patients.

With the use of our remote monitoring detection algorithm a significant (nearly 39%) reduction in total ambulatory flow in the RM group was observed, and there was a numerically higher but not significantly increased number of unscheduled visits in the RM group (36 vs. 22; p = 0.167), but unscheduled in-office visits had a higher ratio of clinically necessary patient evaluations (30 vs. 3 events), mainly driven by pre-emptive medical and device-related ambulatory interventions preventing patients from further worsening of heart failure status and subsequent hospitalization. These findings suggest that unscheduled unnecessary visits have been minimized during RM follow-up, and it is mostly due to higher sensitivity for clinically relevant events. These results let us conclude that there is an increased effectiveness of institutional ambulatory care in this patient group. Furthermore, this novel RM-based follow-up algorithm seems to have the ability to replace most routine ambulatory visits that would not require any intervention.

Limitations

There are some limitations to address in our pilot study.

This investigation was a non-randomized observational study. Remote transmission device availability and patient's decision for remote monitoring follow-up should be taken into consideration when we assess outcomes. Allocation to the RM follow-up arm of the study could improve patient adherence to medication and health improvement targets. These factors might improve outcomes in the RM group, although the 2 selected patient groups did not differ significantly in the most important clinical baseline features.

Conclusion

A novel heart failure detection algorithm based on modified PARTNERS HF criteria adapted to automated, daily data transmission-based remote monitoring-mediated follow-up, early patient contact, and intervention before an impeding heart failure event seemed to be associated with a lower number of heart failure hospitalizations as well as decreased institutional in-office follow-up burden and more efficient ambulatory care.

In our pilot study, remote monitoring-mediated follow-up played a role in the improvement of cardiovascular mortality outcomes compared to conventionally followed CRT-D patients. Further randomized trials with major patient populations are needed to confirm the results observed in our study.

Funding

**Impact of remote monitoring in heart failure patients
with cardiac implantable electronic devices during
COVID-19 pandemic; a single center experience**

Introduction
The outbreak of the coronavirus disease 2019 (COVID-19) had spread into a
pandemic situation affecting healthcare providers around the world. In the
spring of 2020 healthcare systems were warned to potentially decrease the
number of institutional in-office patient evaluations (IPE) to reduce human
contacts and thus potential further spread of COVID-19. In this manner the
pandemic related healthcare restrictions had limited the patients physical
contact to the medical staff.
COVID-19 fundamentally altered healthcare logistics and patient access to
healthcare services.

Expert recommendations emphasized the potential benefits of remote
monitoring in non-CIED heart failure patient group for potential better and
safer patient management during COVID-19 pandemic related healthcare
restrictions and expert position statements were published for reducing in-
office patient evaluation follow-up burden and face-to-face visit events
resulting in potential minimized exposure of patients and healthcare
workers. Some authors suggested consequent activation of RM function in
all newly implanted CIEDs or declared RM as essential in the follow-up of
CIED patients during the pandemic.
Aim of this study was to investigate, whether symptomatic heart failure
patients, with implanted defibrillators (ICD) or cardiac resynchronization
therapy pacemakers (CRT-P) or defibrillators (CRT-D) capable to   remote
follow-up may have clinical benefits in terms of rapid detection of
worsening heart failure or other clinical adverse events compared to a
conventionally followed (non-monitored) patient group during the special
scenario of COVID-19 pandemic.

Methods
Data were retrospectively acquired of 132 patients implanted with single-
or dual chamber ICD, CRT-D or CRT-P devices. All the patients involved in
this study were implanted for at least 1 year before March of 2020 and were
in NYHA II or III functional class at the beginning of the follow-up period.
Device implantations were all performed in consensus with currently
available guidelines of European Society of Cardiology for device therapy
and heart failure. Remote monitoring group (RMG) consisted of 61 patients
whereas conventionally followed group (CFG) consisted of 71 patients.
Follow-up period was 12 months from 15.03.2020 until 15.03.2021. Data
collection was performed in accordance with international regulations

regarding the protection of personal information and data. All subjects gave their informed consent for inclusion before they participated in the study and agreed of anonymous scientific use of their data. The study was conducted in accordance with the Declaration of Helsinki and meets the ethical standards and is in accordance with the guidelines provided by the CPCSEA and World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Humans. The study protocol was approved by the Ethics Committee of the University of Pécs, Hungary (Ethical serial number: 6600/2020).

Patients in the RMG had *Biotronik Home Monitoring*™ or *Medtronic Care Link*™ RPM eligible devices. CFG patients have been implanted with devices from various manufacturers: *Biotronik*™, *Medtronic*™, *Boston Scientific*™, and *St Jude Medical*™ without the capability for RPM function.

Prespecified remote patient monitoring algorithm for worsening heart failure
Home Monitoring™ and *Care Link*™ remote monitoring systems transmit automatically prespecified data to a manufacturer-specific server. The hospitals staff (cardiologists, electrophysiologists, trained nurse) responsible for the patient's care can assess information on a secure website, where the patients are automatically classified and may flagged for clinical attention. Additionally, physicians are notified on prespecified alerts.
Early detection of worsening heart failure was implemented by specific heart failure detection algorithms of Biotronik and Medtronic devices, general considerations are shown on **Figure 9.**
Monitoring data trends and alerting events were revised in weekly frequency. Among CFG patients none of CIED or non-CIED remote monitoring activities were implemented, however patients were contacted on telephone by the device ambulance physician to assess potential complaints on abandoned IPE appointments. Unscheduled in-office visit events were exceptionally arranged on physician or general practitioner referral. In this cases IPEs were strongly complaint and symptom-based in this patient group.
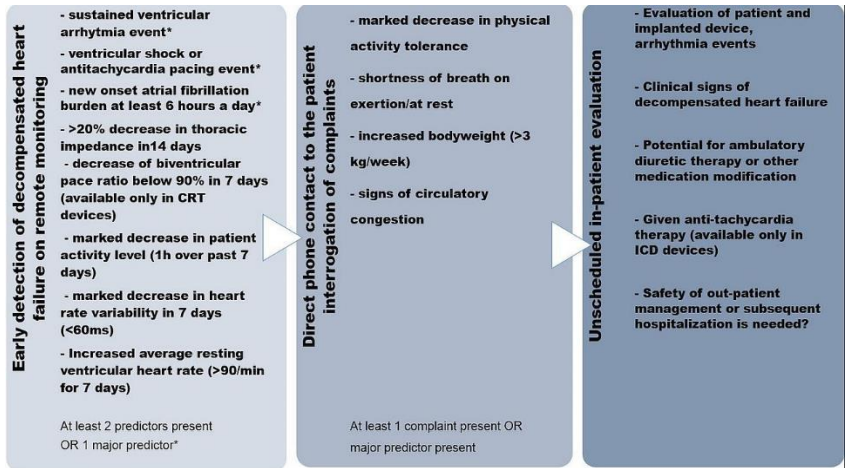
Figure 9. Preemptive detection of worsening heart failure related adverse events with the help of a predefined alert-based workflow. Major criteria in the alert-based detection algorithm were sustained ventricular arrhythmia or ventricular shock event, anti-tachycardia pacing event or new onset atrial fibrillation burden exceeding 6 hours a day. At least two minor detection criteria positivity resulted in a consecutive telephone contact to the patient. Unscheduled in-office patient evaluations were arranged at major criteria positivity and/or at least 2 minor criteria positivity and presence of patient complaint.

Statistical analysis

The sample size calculation was based on a hypothesis, with a 25% margin for the occurrence of heart failure, arrhythmia and device related adverse events at 12-month follow-up assumed. Pre-set values were 5% for the significance level and 80% for the power. A required sample size of (54+54) 108 patients with complete datasets was calculated in an observational study design. After considering rate of incomplete data sets (predicted at approximately 10 %), a total of ~130 patients were planned for recruitment. All follow-up variables were divided to categorical or continuous variables. Data are presented as mean ± standard deviation for normally distributed continuous variables, median (25th and 75th percentiles) for non-normally distributed variables, or percentages for binary variables. Missing data were not replaced; all available data were used for sample distribution evaluation. Normality was checked with the Shapiro-Wilk test. For normal distributed data Student t test was used. Mann-Whitney test was used for inter-individual comparisons of continuous variables, when normality was rejected. Categorical variables were compared with the Chi-square or

Fishers exact test. For primary endpoint outcome an adverse event free survival analysis was applied in Kaplan–Meier's survival curve estimation with log-rank test. Spearman's Rho correlation test was performed and binary logistic regression analysis were performed to confirm statistically significant correlations.

Statistical analysis was performed using IBM SPSS statistical software version 25.0. (Armonk, NY, IBM Corp.). The level of significancy was defined as p< 0.05.

Results

Patient populations

61 patients in the remote monitoring group (RMG) and 71 patients in the conventionally followed group (CFG) were involved in this observational study. Baseline patient characteristics of the two patient-groups are shown on **Table 6**.

	Remote monitoring group (RMG), n= 61	Conventionally followed group (CFG), n=71	P value
Age (years), median (IQR)	72.0 (61.5-77.5)	71.0 (59.0-77.0)	0.549
Sex (male/female)	46 / 15	54 / 17	0.931
Single chamber ICD, n (%)	27 (44.3)	29 (40.8)	0.291
Dual chamber ICD, n (%)	7 (11.5)	17 (23.9)	
CRT-defibrillator, n (%)	18 (29.5)	22 (30.1)	0.854
CRT-pacemaker, n (%)	9 (14.6)	3 (4.2)	**0.037**
ICD for secondary prevention of SCD, n (%)	16 (26.2)	17 (23.9)	0.763
Implantation time before study inclusion months (mean±SD)	26.5±10.3	28.3±12.4	0.831
Comorbidities:			
Hypertension, n (%)	55 (90.2)	56 (78.9)	0.078
Diabetes, n (%)	30 (49.2)	34 (47.8)	0.235
Dyslipidemia, n (%)	33 (54.1)	36 (50.7)	0.297
Atrial fibrillation, n (%)	24 (39.3)	22 (32.4)	0.410
NYHA class, n (%)	II: 16 (26.2)	II: 48 (66.2)	**< 0.001**
	III: 45 (73.8)	III: 23 (33.8)	
Chronic kidney disease, n (%)	15 (24.6)	12 (16.9)	0.277
Chronic lung disease, n (%)	12 (19.7)	15 (21.1)	0.837
Ischemic heart disease, n (%)	39 (63.9)	43 (60.6)	0.692
Previous myocardial infarction, n (%)	33 (54.1)	18 (25.4)	**0.001**
Previous open-heart surgery	18 (31.6)	21 (32.4)	0.922
LV systolic function/diameter:			
LVEF, median (IQR)	35.0 (30.0-48.0)	38.0 (31.0-45.0)	0.073
LV EDD, median (IQR)	62.0 (54.00-65.0)	59.0 (56.0-68.5)	0.980
LV ESD, median (IQR)	45.0 (43.0-50.0)	45.5 (41.0-50.5)	0.852
Medications:			
ACEi/ARB (%)	95.1	80.28	**0.048**
ARNI (%)	4.9	12.7	**0.036**
BB (%)	95.1	100.0	0.065
MRA (%)	59.0	59.1	0.32
Amiodarone (%)	34.4	36.8	0.201
Antiplatelet agent (%)	55.7	38.2	**0.047**
OAC (%)	44.3	47.1	0.751
Statin (%)	55.1	43.6	**0.041**

Table 6. Baseline patient parameters *Abbreviations: ICD:implantable cardioverter defibrillator ; CRT: cardiac resynchronization therapy; SCD: sudden cardiac death; NYHA: New York Heart Association; LV: left ventricular; LVEF:left ventricular ejection fraction ; EDD:end-diastolic diameter ; ESD:end-systolic diameter ; ACEi:angiotensin converting enzyme-inhibitor ; ARB:angiotensin receptor blocker ; ARNI:angiotensin receptor blocker/nephrilysin inhibitor ; BB:beta receptor blocker; MRA: mineralocorticoid receptor antagonist; OAC: oral anticoagulant*

Burden of in-office patient evaluations during COVID-19 pandemic

During the first 6 months of COVID-19 pandemic (15.03.2020 – 15.09.2020) the number of total in-office patient evaluations (IPE) in in our cardiac device ambulance decreased to 72% of the year before (1590 IPE to 1224 IPE; p= 0.032) and the total IPE number remained significantly decreased in the second 6 months (16.09.2020 – 15.03.2021) as well with 88% of the investigations and device interrogations the year before (1581 IPE to 1392 IPE).

There were 37 IPE; 0.606 IPE/patient in RMG and 42 IPE; 0.591 IPE/patient in the CFG during the 12 months of follow-up period as shown on **Table 7**. No differences were observed in abandoned scheduled IPEs (0.6557 IPE/patient vs. 0.6197 IPE/patient; p= 0.633) or urgent, unscheduled IPE events (0.6065 IPE/patient vs. 0.5915 IPE/patient; p= 0.855).

Adverse event rates and hospitalization for heart failure

No statistically significant differences were seen neither at first 6 months (p=0.214) nor 12 months (p=0.672) in the primary composite end-point of device related-, arrhythmia- or worsening heart failure related adverse events between the two observed patient groups. Kaplan-Meier curve represents adverse event-free survival in the investigated patient groups during the observational period as shown on **Figure 10**.

Worsening heart failure events in the RMG showed a statistically not significant but increased tendency (0.231 event/patient vs. 0.145 event/patient; p=0.069) in the first 6 months of COVID-19 pandemic. In-spite of the upper tendency, the hospitalization numbers for worsening heart failure in the first 6 months of the pandemic were significantly lower in the RMG (0.016 event/patient vs. 0.169 event; p=0.012) than in CFG. (**Table 7.**)

Notably; patients with worsening heart failure event in CFG requiring in-office patient evaluation and/or hospitalization had significantly increased N terminal-proBNP (brain natriuretic peptide) levels (15529 ±362 pg/ml in CFG vs. 9762±368 pg/ml in the RMG; p=0.01>) and more deterioration from baseline NYHA functional class than patients in RMG (mean ΔNYHA

in RMG: 0.65±0.12 vs. mean ΔNYHA in CFG: 1.32±0.96; p = 0.026) as shown on **Figure 11. A** and **B.**

	COVID-19 pandemic first 6 months			COVID-19 pandemic at 12 months		
	RMG	**CFG**	p	**RMG**	**CFG**	p
Arrhythmia and device related event (event/patient)	0.131	0.14	0.132	0.146	0.169	0.699
Arrhythmia and device related hospitalization (event/patient)	0.049	0.07	0.629	0.131	0.098	0.547
Worsening of heart failure event (event/patient)	0.231	0.145	0.069	0.328	0.267	0.151
Worsening of heart failure related hospitalization (event/patient)	0.016	0.169	**0.012**	0.115	0.225	0.096
Total in-office patient evaluations (event/patient)	0.262	0.253	0.98	0.606	0.591	0.959

Table 7. Event rates in patient groups at 6 and 12 months of follow up
Abbreviations: COVID-19: corona virus disease 2019, RMG: remote monitoring group, CFG: conventionally followed group.
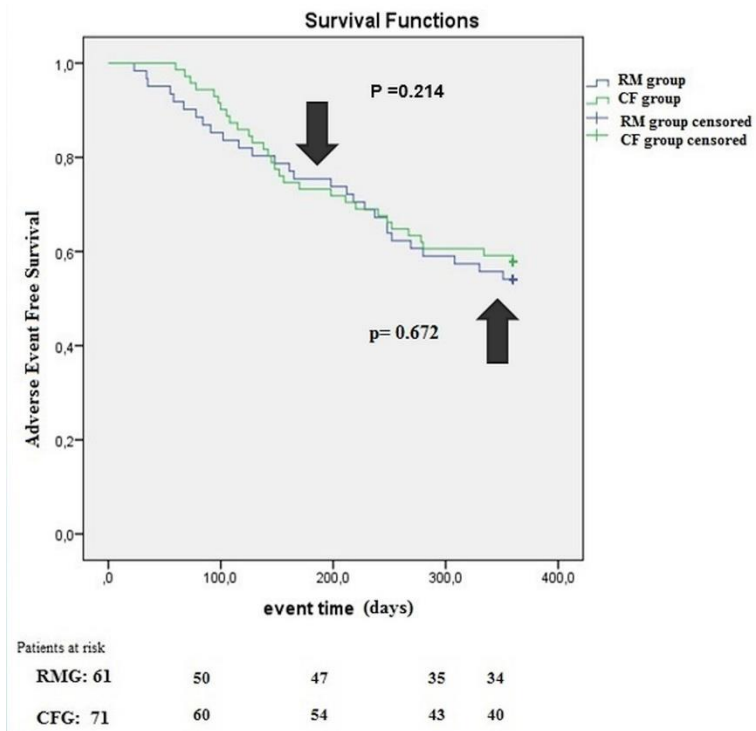
Figure 10. Kaplan-Meier's curve: Adverse event-free survival. The composite end-point of device-, arrhythmia and worsening heart failure related adverse event-free survival is statistically non-differing in the two observed patient groups neither at 180 days (log rank p=0.214) nor at 360 days (log rank p=0.672) of follow-up during the COVID-19 pandemic.
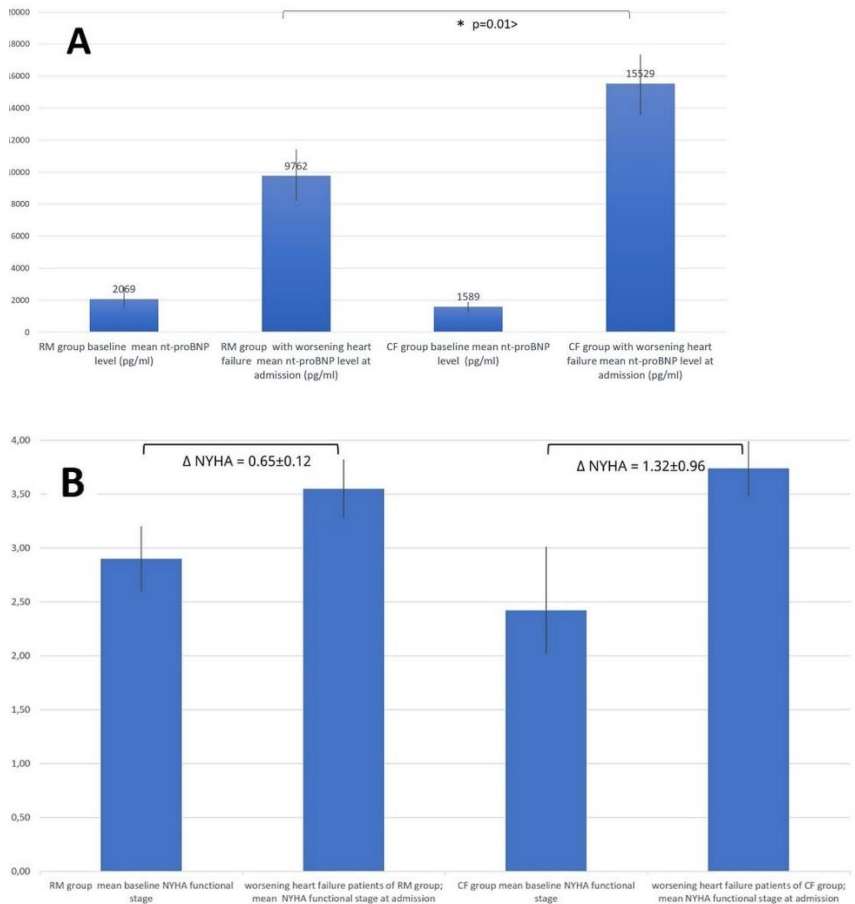
Figure 11. Comparison of NT-proBNP levels (A) and change in NYHA functional class (B) at baseline and hospital admissions for worsening heart failure in the remote monitoring (RMG) and conventionally followed (CFG) patient groups.
Patients in the conventionally followed group (CFG) had a significantly increased NT-proBNP (brain natriuretic peptide) levels at worsening heart failure event related hospital admissions (15529 ±362 pg/ml in CFG vs. 9762±168 pg/ml in the RMG; p=0.01>) and more pronounced deterioration from baseline NYHA functional class than patients in remote monitoring group (RMG) (mean ΔNYHA in CFG: 1.32 vs. mean ΔNYHA in RMG:0.65; p = 0.026).

Correlational analysis

It has to be emphasized, that patients with specified remote monitoring alert-based follow-up scheme had independently lower risk for heart failure hospitalization (p=0.045) in the observed 12 months of pandemic period.

Discussion

Significant number of IPEs in device clinics were abandoned worldwide during COVID-19 pandemic, thus patients with automatic transmission based remote monitoring surveillance had potential advantage in the timely detection of clinically relevant adverse events with the help of previously developed alert-based follow-up models. Few of these remote follow-up modalities offer preemptive detection of worsening heart failure status of the patient.

The primary end-point of our observational study was to assess the composite end-point of arrhythmia, device and worsening heart failure related adverse events in the two patient cohorts. These event rates were higher in our patient groups compared to an observational study which combined anti-bradycardia, ICD and CRT implanted patients during the SARS Cov-2 pandemic related lockdown in Italy. Patients involved in our study had more advanced heart failure, this may explain relative higher observed adverse event rates. In addition, the two involved patient populations in our study were non-homologous in terms of baseline patient comorbidities, heart failure conditions and medications. Patients in RMG had worse baseline NYHA heart failure functional class and fewer patients were on ARNI (angiotensin receptor blocker/nephrilisin inhibitor) therapy. RMG patients had tendentiously higher risk for worsening heart failure event in the first 6 months of COVID-19 pandemic, where institutional restrictions were the most pronounced with a significant 28% decrease in the device interrogations and heart failure IPE numbers. Although tendentiously higher heart failure deteriorations were observed, these patients had only modest increase in NT-proBNP levels and suffered less deterioration in NYHA functional class compared to CFG patients. These results let us conclude that RMG patients who had worsening of heart failure had accelerated institutional detection and admission time. Preemptive detection and early pharmacological/non-pharmacological interventions at IPEs efficiently prevented further progression in heart failure status and hence reduced hospitalizations driven by decompensated heart failure. At 12 months follow-up time the upper seemed benefits in the RMG diminished and it might be explained by the baseline relevant differences between the two patient populations.

Conclusions

We can conclude that alert based remote monitoring of CIED patients with advanced heart failure in our observational study enabled preemptive

detection and fast clinical intervention at impeding cardiac decompensation events. Remote monitoring seems to play promising role in reducing the burden of heart failure hospitalizations even in pandemic circumstances. Further observational trials with larger patient populations are needed to confirm our findings.

Funding

V. Summary of the new scientific results

1. Automatic daily remote monitoring in heart failure patients implanted with cardiac resynchronization therapy-defibrillator; a single center observational pilot study

In our pilot study we tested our institutional remote monitoring protocol which was based on modified PARTNERS HF criteria system for capability of early detection of decompensated heart failure in CRT-D implanted patients. Early ambulatory interventions were performed to prevent hospitalization events for worsening heart failure, and patient-death associated with heart failure events.

Our study firstly publishes the following results at the same remote monitored patient group:
- lower cardiovascular death rate during 25 months of follow-up period compared to conventional followed patients
- decreased hospitalization for decompensated heart failure in the remote monitored patient group
- more effective and decreased institutional ambulatory burden of remote monitored patients in-spite of above-mentioned results

Although the above results are clear, taken into consideration patient sample size and follow-up length, further prospective randomized trial with larger patient population would be needed to confirm the efficacy of our novel RM follow-up algorithm in HF patients implanted with CRT-D devices.

2. Impact of remote monitoring in heart failure patients with cardiac implantable electronic devices during COVID-19 pandemic; a single center experience

Based on our study-hypothesis patients followed with remote monitoring have beneficial advantage in terms of more effective patient surveillance. Thus, preemptive and adequate ambulatory interventions at early worsening heart failure state may have the potential to successfully prevent hospitalization events for worsening heart failure in the remote monitoring group.

Our study firstly publishes the following results in a remote monitored advanced heart failure cardiac implantable device patient group during COVID-19 lockdown:

- Less deterioration in heart failure regarding functional capacity and biomarker level elevation (NT-proBNP) in the remote monitored patient group at hospital patient evaluations compared to conventional followed patients; suggesting earlier detection of worsening heart failure in the remote monitoring group.
- Significantly decreased hospitalization rate for worsening heart failure during the first 6 months of COVID-19 lockdown in remote monitored patient group.

This observational study included two patient populations that were non-homologous in terms of baseline comorbidities. Further observational trials with larger patient populations are needed to confirm our findings.

VI.   Acknowledgement

VII.   Publications of the author

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