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

Phd Dissertation

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1. 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

2. Introduction

2.1. Relevance of heart failure patient monitoring

Heart failure (HF) is an evolving public health issue in Europe and in the United States [1]. Despite pharmacological and non-pharmacological therapeutic advances, the rates of hospital admissions for HF means high burden for healthcare providers. Furtheron; a significant proportion of HF patients are readmitted to the hospital after insitutional 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 [2].

Patients are usually admitted to the hospital because of worsening heart failure symptoms, such as significant decrease in fucntional capacity, signs and symptoms of congestion or low-cardiac output syndrome. Symptoms of cardiac decompensation are often associtated with increased filling pressures of 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 parmacological/ non-pharmacological interventions may have the potential to effectively prevent worsening heart failure patients from hospitalization.

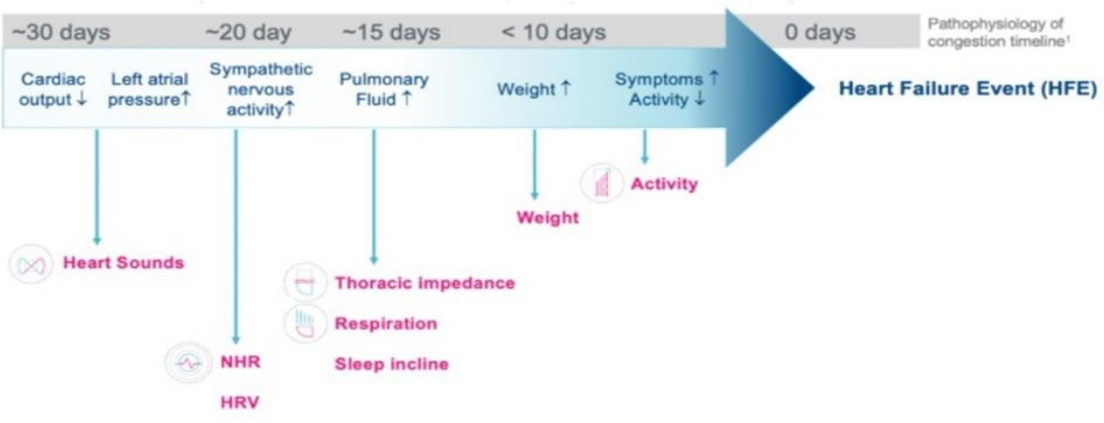

Figure 1. Evolving changes in cardiac physiology and hemodynamics during worsening of heart failure. Patophysiological changes of certain physiological parameters may preemptively warn for an upcoming cardiac

decompensation event even weeks before apparent signs and symptoms of circulatory congestion.
Source: www.bostonscientific.com/electoroppysiology/heartlogic

Nowadays avalibility of monitoring of several physiologcal parameters are given in cardiac implantable electornic device (CIED) wearing heart failure patients, these parameters can have serious impact in the follow-up and clinical outcomes of these patients.
In the eraly 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 variabilty, patient activity, arrhytmia events) related to the exacerbation of HF aswell. Further step in patient-device remote monitoring was made by the installation of algorithms measuring the patients intrathoracic impedance. Monitoring of these parameters have role in the predilection and early detection of worsening heart failure [3].
Domestic cardiological literature serves aswell with excellent summarizing article regarding the utilization of different remote monitoring systems in clinical practice [4].

2.1. 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 intervalls using either analog or digital landlines or nowadays more preferably wireless data networks.
Remote monitoring of devices provides continuous survellance of device integrity and shows wheter clinically relevant event for the patient occured. In case of device integrity problems or significant alterations in the patients 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.

Recently, remote patient management (RPM) based follow-up was introduced and declared and standardized in an internationally accepted expert consensus document [5].

Two relevant forms of RPM are known:

- Remote monitoring provides continuous monitoring and data transmission based on preprogrammed time interval. Remote monitoring is defined as automatic transmission of a triggered alert.
- Remote interrogation or remote follow-up can replace in-office patient evaluations aimed at evaluating device integrity (battery status, lead impedance, sensing, threshold) as a scheduled automatic device interrogation.

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. [6] **Table 1**. summarizes characteristics of different remote monitoring systems according to manufacturers.

The General Data Protection Regulation (GDPR) by the European Union provides legal framework concerning the collection and processing of personal private informations. Collecting and retaining data should be limited and specified between the hospital and the manufacturer. Cybersecurity is ensured by all device manufacturers regarding data transfer to the server and the hospital.

2.2. Role of thoracic impedance monitoring

Accumulation of fluid in the lungs and pulmonary circulation leads to meaningful decrease in the electric impedance in the chest cavity. Thus, pulmonary congestion can be detected by measuring progressive changes in thoracic impedance values. Fluid facilitates the conductance of an electrical current, resulting in a corresponding decrease in impedance at accumulation. By sending constant current through the right ventricular pacing electrode at stimulation to the device box, thoracic impedance can be acquired from the electrical pathway (chest cavity tissues) constructed between the pacing electrode and the device can.

The first study which was designed to evaluate thoracic impedance measurements was the Mid HeFT (Medtronic Impedance Diagnostics in Heart failure) study. In this investigation thoracic impedance showed strong correlation with pulmonary capillary wedge pressures in hospitalized patients [7]. In the same study 60 Ohm of nominal threshold of impedance was used to define a

Table 1. Comparison of different remote monitoring systems. Based on Zima E. et al [4].
GPRS: General Pocket Radio Service, 3G: third generation internet network, IEGM: intracardiac electrocardiogram.

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™)	

patient population with early warning for pulmonary congestion before hospitalization for heart failure with a sensitivity of 77%. These results were used to develop OptiVol™ algorithm (Medtronic, Minneapolis, USA).

The performance of intrathoracic impedance monitoring for the prediction of HF events in chronic HF patients was further evaluated in the prospective double blinded SENSE-HF (Sensitivity of the InSynch Sentry OptiVol feature for the prediction of Heart Failure) study. This study demonstrated a sensitivity of 42% and positive predicting values of 38% for HF events with a dynamic performance after 6 months of device implantation [8].

The randomized, controlled DOT-HF (Diagnostic Outcome Trial in heart failure) investigated whether thoracic impedance monitoring and other device-based diagnostic information could

improve outcomes in patients with HF. Patients were randomized to a monitored and non-monetarized group. There was a significant increase in the number of additional in-office patient evaluations and hospitalizations for heart failure in the monitored patient group compared to the control arm. In contrast, relatively more sings of HF among control patients were observed during in-office visits. Specificity of intrathoracic impedance monitoring alone in detecting HF event was poor, leading to false positive alerts, increasing the ambulatory IPE burden and number of unnecessary in-office visits, further on this monitoring method induced higher number of HF hospitalizations than in the control group [9].

Multiple vector analysis of the thoracic impedance is might be a solution for further increasing the performance of this monitoring method alerting in the early phases of pulmonary fluid accumulation and congestion. St Jude Medical CorVue™ multivector intrathoracic impedance monitoring system utilizes right- and left sided electrode stimuli to measure intrathoracic impedance values (St Jude Medical, Sylmar, USA) [10]. This algorithm was shown to have 62-72% of sensitivity for detecting early signs of congestion in the pulmonary tissues, but the false positive alert rate (0.56 – 0.6 event/patient/year) remained high.

Recently published multicenter prospective DEFEAT-PE study (Detect Fluid Early from Intrathoracic Impedance Monitoring) evaluated the safety and effectiveness of multivector intrathoracic impedance measurements based CorVue™ algorithm. The multiple vector thoracic impedance measurement based algorithm resulted in a low sensitivity of 21% and a false positive rate of 0.9 event/patient/year [11]. Despite using multiple vectors to detect changes in thoracic impedance the clinical impact of this algorithm is strongly limited.

Taken together, the diagnostic efficacy of monitoring intrathoracic impedance for early detection of heart failure decompensation alone is poor, both for single vector and multiple vector algorithms.

2.3. 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 [12]. 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. In a post-hoc analysis patients in the high-risk group were 10 times more likely to have an HF hospitalization in the next 30 days compared to those in the low-risk group. 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 [13].

Recently, MultiSENSE study (Multisensor Chronic Evaluation in Ambulatory Heart Failure Patients) evaluated several physiological parameters related to exacerbation of HF. [14] These parameters included heart sounds indicating ventricular chamber fillings, respiratory count, thoracic impedance, heart rate and physical activity which were used to construct a composite index and alert algorithm (HeartLogic™, Boston Scientific). In the MultiSENSE study, the algorithm effectively detected 70% of worsening heart failure events median early warning of 34 days before HF event. Further clinical experience of multiparametric remote monitoring with the help of HeartLogic™ algorithm was described in a retrospective case series report.[15]

Daily HeratLogic index data of 58 patients was analyzed on a 5 months follow-up term. During follow-up time a default HF index threshold was met 16 times in 24 patients, yielding 0.99 alert/patient/year. The median early warning time was 38 days int he case of hospitalizations and

12 days in that of minor HF event reflecting the clinical deterioration of heart failure. In this early experience this algorithm demonstrated its ability to detect gradual worsening of heart failure. Currently MANAGE-HF (Multiple Cardiac Sensors for the Management of Heart Failure) a multicenter, open-label, prospective, multi-phase trial has been closed and phase I. results have been recently published. MANAGE-HF enrolled 200 patients with CRT-D/ICD devices capable for HeartLogic heart failure diagnostics. This algorithm demonstrated safety integrated in clinical practice. Based on the algorithms preemptive heart failure alert diagnostics prompted augmentation of HF medication (mostly diuretics) the study was closed with a 67% reduction in HF hospitalizations compared to a pre-alert 12 moths follow-up period of the same patient population. This trial is recruiting patients now for further evaluation of the performance of HeartLogic-alert based management in improving mortality and morbidity from HF in routine care (NCT03237858).
Both PARTNERS-HF and MultiSENSE studies showed promising results, but in order to further assess the performance of these algorithms in clinical practice, larger studies are needed.

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. Recently D'Onofrio et al. introduced a validated multiparameter monitoring based prediction algorithm for heart failure hospitalizations in SELENE HF (Selection of potential predictors of worsening heart failure) trial [16]. A baseline risk-stratifier Seattle HF Model was combined with temporal trend of various physiological (diurnal- and nocturnal heart rate, heart rate variability, physical activity) arrhythmia (ventricular extrasystoles, atrial fibrillation burden) and thoracic impedance parameters. Reaching the nominal index threshold of the algorithm, patients had substantially increased risk for heart failure hospitalization. The algorithm was showed to have an 65.5% sensitivity for an upcoming heart failure event with acceptable false/unexplained alert rate of 0.69 alert/patient/year. **Figure 2.** shows SELENE-HF Biotronik Home monitoring variable trends for predicting HF event.

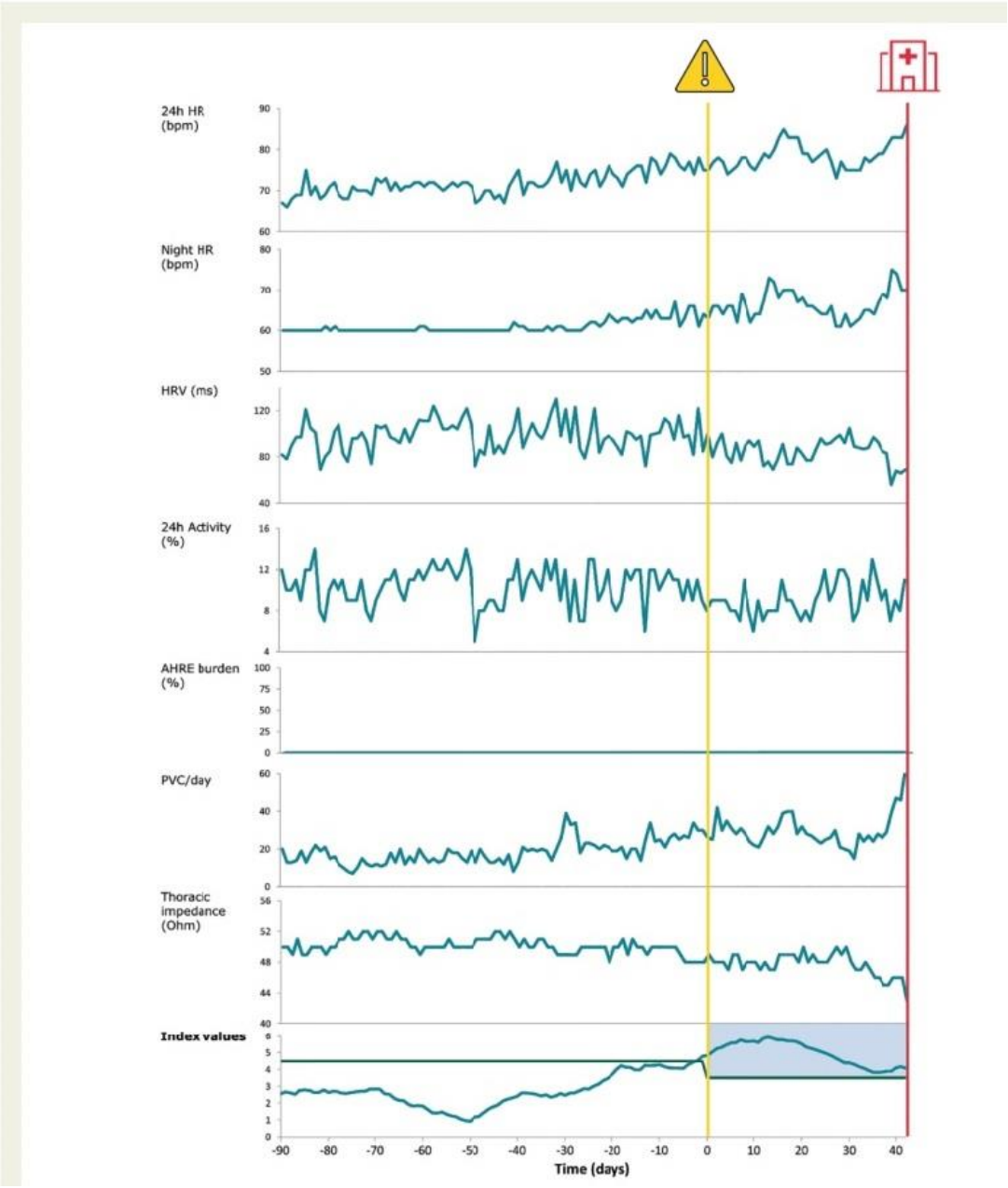

Figure 2. Home monitoring™ variables predicting heart failure event.

Seattle HF questionnaire baseline HF risk stratification and continuous monitoring of variables equals a HF score system. If a patient is reaching the index threshold score, hospital staff is warned through a remote server for a higher risk for an impeding HF event. This algorithm can predict worsening of heart failure even 4-6 weeks before hospital admission. In the above example, the alert would have allowed a proactive care and possibly prevent the exacerbation of HF. *Source: D'Onofrio et al. Combining home monitoring temporal trends from implanted defibrillators and baseline patient risk profile to predict heart failure hospitalizations: results from the SELENE HF study. Europace. 2022 Feb 2;24(2):234-244.*

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*

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

2.4. 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 [17-25]. The total number of patients enrolled in these trials was 8326. The mean age was 62 to 70 years with the proportion of male patients ranging from 71% to 88%. The mean left ventricular ejection fraction (LVEF) ranged from 25% to 35% and the proportion of patients with ischemic cardiomyopathy ranged from 44% to 70%. The mean follow-up time ranged from 12 to 34 months (**Table 2.**)
Majority of these trails also performed telemedicine-based disease management strategy telephone interviews or even unscheduled in-office patient evaluations.
A total of 8 trials with 6329 patients reported on all-cause mortality. The risk ratio (RR) for all-

cause mortality with remote monitoring mediated follow-up was not statistically significant from in-office visit mediated follow-up. 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) [21]. Meta-analysis by Parthiban et al. examined the effect of competing remote monitoring technologies on all-cause mortality [26]. 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 [27].

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 REM-HF trial (The Remote Management of Heart Failure using implantable electronic devices) is the largest study with the longest follow-up period on remote monitoring in HF. In this trial, no alert-based strategy was used. Changes in monitored parameter trends were reviewed with weekly frequency. A total of 1650 patients were randomized and enrolled to remote monitoring or conventional (in-office follow-up based) care. The median follow-up time was 2.8 years. The investigators found no reduction in the risk of all-cause mortality or hospitalization for cardiovascular reasons with management guided by weekly active remote monitoring as compared to conventional care (RR: 1.01; 95% CI: 0.87 to 1.18; p= 0.87) [28].

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 [29, 30]. 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.

However, a recently published post-hoc analysis could not support the role and importance of remote monitoring among atrial fibrillation patients in the REM-HF study group. In addition, the risk for hospitalization was increased for any cardiovascular cause in the remote monitoring patient group, mainly driven by more worsening of HF hospitalizations in patients with permanent AF [31].

Discrepancy between the outcomes of the IN-TIME and REM-HF trials can be explained by several aspects of the two trial's patient populations.

Considering baseline clinical characteristics, patients enrolled in the IN-TIME trial had more advanced HF compared to those in REM-HF trial, lower mean LVEF (26% vs. 30%) and more patients had worse NYHA functional class.

Secondly, patients with permanent AF were excluded in IN-TIME, while this was not an exclusion criterion in REM-HF trial. The higher proportion of patients with permanent AF in REM-HF may have weakened the beneficial effect of remote monitoring. Patients with paroxysmal or persistent AF could derive more benefits from remote monitoring by improving ventricular rate control or restore sinus rhythm.
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**.

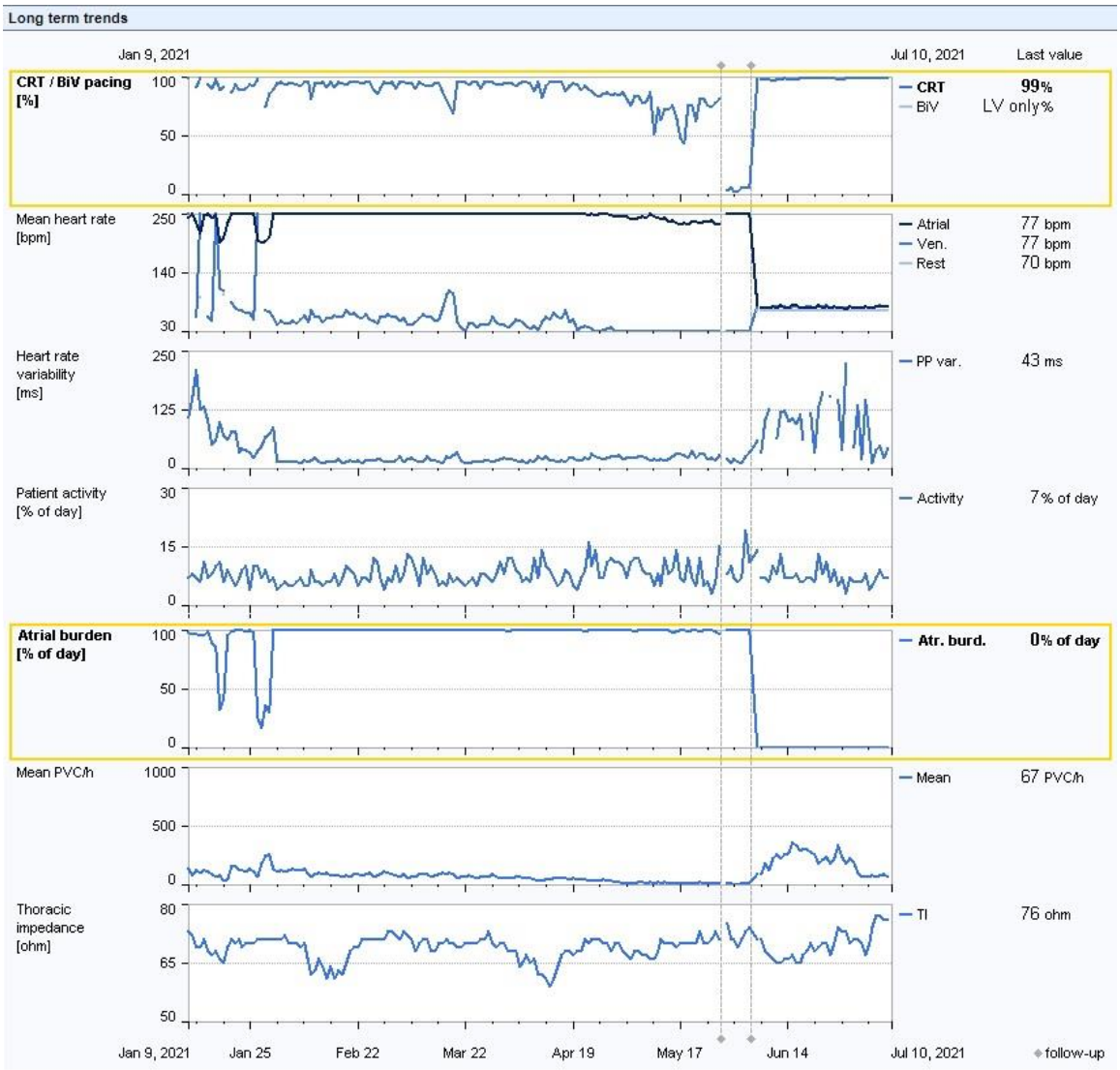

Figure 3. Biotronik Home Monitoring™ heart failure monitor.

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).

2.5. 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 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

Studies investigating the performance of thoracic impedance and/or multiparametric remote monitoring efficiency in CIED implanted HF patients served with ambiguous evidence.

Further on, 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.

Seen these advances we have to count with further technological progress as well. Recent studies with CardioMems™ (Abbott, USA) invasively implanted pulmonary artery pressure monitor can aid physician to prevent worsening of heart failure, improve quality of life and decrease HF related mortality mainly through preventing HF linked hospitalizations according to 4 prospective trials totaling over 3000 patients. This latter technology has the potential to indicate early pressure increase in the pulmonary artery in any form of left-sided heart failure, independently of left ventricular ejection fraction (reduced: LVEF<40%, mildly reduced: 40-50% or preserved: LVEF>50%). The presymptomatic data provided by the CardioMEMS HF System allows proactive changes in medical therapy before heart failure related symptoms appear [32- 38].

3. Focus and aim of the studies

3.1. 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.

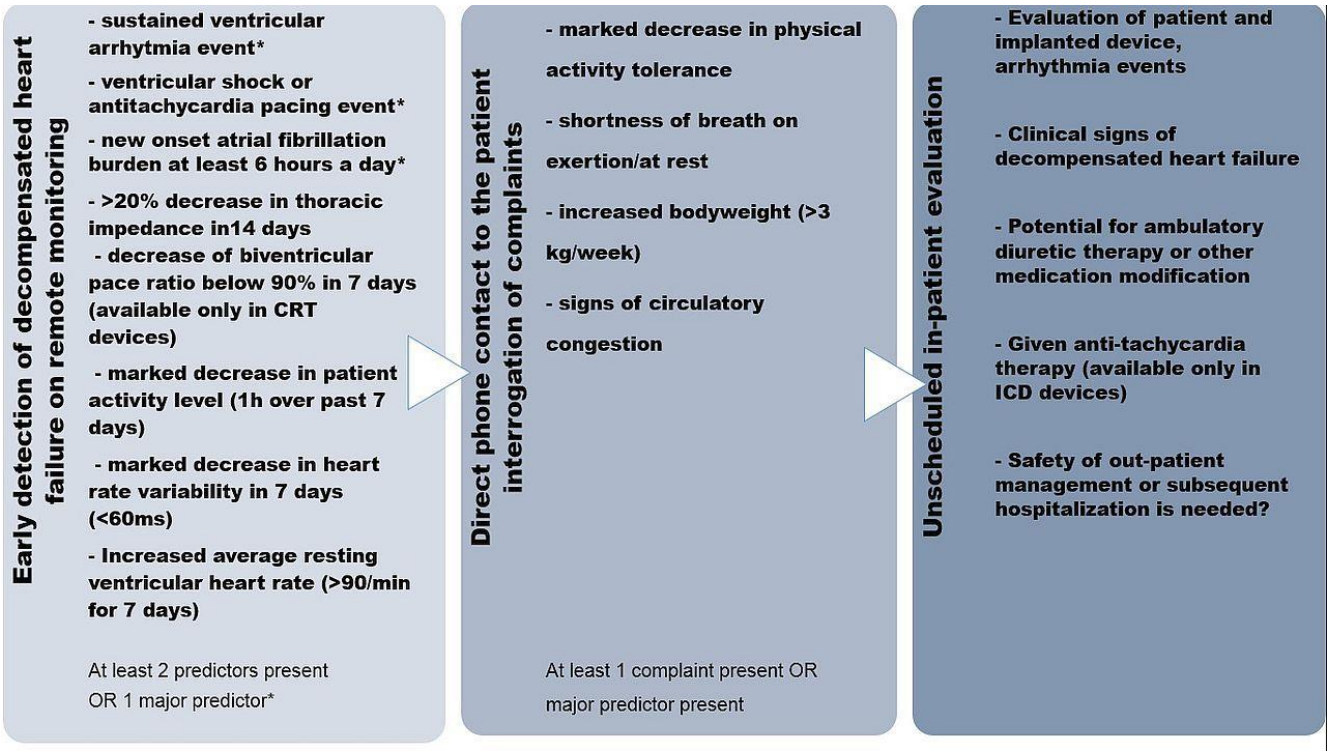

Figure 4. Institutional algorithm and workflow for preemptive detection of HF

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 retrospective observational study, we aimed to investigate clinical outcomes like cardiovascular (CV) mortality, hospitalization for CV cause; especially hospitalization for worsening HF. We designed the study to assess clinical ambulatory burden in this patient group and ratio of unscheduled, clinically necessary ambulatory 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.

3.2. Potential impact of remote monitoring during the COVID-19 pandemic

Possible clinical benefits of remote monitoring could not be more actual than during a pandemic situation. In the spring of 2020 healthcare systems, all over the world were warned to potentially decrease the number of institutional IPEs to reduce human contacts and thus potential further spread of coronavirus disease 2019 (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, further on; considerable number of in-office patients visits were abandoned during the intermittent institutional restrictions during the pandemic waves.

Expert consensus statements emphasizing the role of remote monitoring and care to potentially decrease ambulatory burden in healthcare institutes during COVID-19 pandemic [39- 43]. Some authors recommended consequent activation of remote monitoring and remote patient management service abilities and declared their role in the current pandemic situation of essential [44-46].

In this manner, we designed an observational study to assess potential clinical benefits of remote monitoring in a CIED implanted HF patient group compared to a conventional followed device implanted HF patient group.

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

4.1. Introduction

Cardiac resynchronization therapy (CRT) provides an evidence-level treatment manner in a well selected subgroup of patients with advanced systolic heart failure and functional dyssynchrony. CRT is a proven method to reduce symptoms, morbidity (hospitalizations), and mortality in heart failure patients responding or super-responding to therapy [47, 48]. Remote monitoring of patients with cardiac implantable devices (CIED) in heart failure has an established recommendation according to the currently available heart failure guidelines of the European Society of Cardiology (ESC) [49]. Cardiac resynchronization therapy-defibrillators (CRT-D), capable of remote monitoring (RM) function, transmit numerous measurable patient- and device-related data on a predetermined time basis or even immediately if a critical event is observed by the implanted device. Detection alerts and transmission algorithms depend on the manufacturer of the system.

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) [50–54]. 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 [54–56]. The PARTNERS HF study investigated 694 CRT defibrillator patients with remote monitoring and continuous multi-parameter monitoring for heart failure. Monthly review of monitored parameters and patients with positive combined heart failure diagnostics of long-lasting atrial fibrillation and/or high ventricular rate, low biventricular pacing ratio, abnormal autonomic signs (elevated resting heart rate, low heart rate variability), decreased patient activity, and high thoracic fluid index had a 5.5-fold increase in the risk for heart failure hospitalizations within the subsequent month. Evaluation of heart failure device diagnostics more frequent than one week improved the ability to risk stratify patients for subsequent heart failure events [12]. Although previous results are well proven, the exact alerting thresholds for each detection parameter are still debated, and a novel heart failure detection algorithm and effective intervention are highly warranted to prevent

worsening heart failure-related hospitalization and death. Remote monitored heart failure patients implanted with cardiac implantable devices (CIEDS) show contradicting outcome results regarding survival, hospitalization, and institutional ambulatory burden in prospective randomized studies and meta-analyses [21, 25, 26, 57, 58]. Nevertheless, several trials proved an equivocal decrease in institutional ambulatory burden and cost-effectiveness in the care of remote monitored patients [3, 17, 59-62]. 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.

4.2. Material and Methods

4.2.1. Study design

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 [49]. 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. The opportunity for remote monitoring and device remote follow-up was offered to every patient before implantation if an RM eligible Iforia device and Cardiomessenger device were available at the same time. Remote transmission device availability was the main selection criterion, whether a patient was followed with remote monitoring or not.

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). Biotronik devices with a Home Monitoring remote monitoring system were chosen for the retrospective analysis because the system provides daily transmission based automatic remote monitoring, and the specific device was the most available in our institute at the time of device implantations. 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. **Table 3.** presents the parameters that were assessed at remote interrogation and/or in-office ambulatory follow-up events. Data regarding CV mortality, cardiovascular hospitalizations, institutional admissions for decompensated heart failure, ambulatory patient flow, baseline characteristics, medications, and comorbidities were collected from patient files, remote interrogations of the device, and from an integrated patient care information system of University of Pécs. 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).

Table 3. Parameters assessed at remote interrogation and in-office follow-up.

Parameter type	
Current rhythm diagnosis and pacemaker dependency	Therapy given for sustained ventricular arrhythmia (anti-tachycardia pacing, ventricular shock) *
Mean ventricular heart rate*	Biventricular pacing ratio*
Battery lifetime expectancy	Inappropriate ventricular shock events*
Lead impedance/ shock lead impedances	Review of device triggered alert events*
Pacing thresholds for different electrodes	Patient activity level*
Sensing signal amplitude threshold for different electrodes	Heart rate variability*
All arrhythmia events (atrial arrhythmia burden, ventricular extrasystoles and other arrhythmia events) *	Intrathoracic impedance status*

**Parameters influencing heart failure status management*

4.2.2. Study endpoints

The primary objective of this study was to compare the CV mortality of remote-monitored patients with patients on a conventional follow-up scheme. Survival was assessed as the time from CRT-D implantation to a CV mortality event. Secondary endpoints were the number of cardiovascular hospitalizations, expressively the number of hospitalizations for decompensated heart failure. Further secondary endpoints were the total number of ambulatory visits, and the ratio of unnecessary ambulatory visits in each patient group during follow-up.

4.2.3. 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 [12] 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. [13] 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 4.** 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. Our institutional criteria-protocol for screening remote monitored patients with impeding status for decompensated heart failure is shown on **Figure 4**.

Table 4. Comparison of refined PARTNERS-HF [13] and remote monitoring criteria for predicting decompensated heart failure event in our institute.

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

AF: atrial fibrillation

4.2.4. Ambulatory visit definitions

Patient flow at our institute was assessed with respect to all ambulatory visits in both patient groups, divided into scheduled, unscheduled necessary, and unscheduled unnecessary ambulatory visit events. Scheduled ambulatory visits were always in the form of a prearranged ambulatory appointment at least once a year in the RM group and every 3 to 6 months in the CFU group. Unscheduled ambulatory in-office visits only occurred in the RM group if at least 1 major RM criteria for heart failure or at least 2 minor criteria with even modest heart failure symptoms at patient interrogation occurred.

These patients were urgently contacted, and a pre-emptive unscheduled ambulatory visit was arranged. Patients in the CFU group were checked at scheduled visits; unscheduled visits were only set up based on general physician referral, emergency physician referral, or severe patient complaints. Unscheduled ambulatory visits qualified as unnecessary in-office visits were visit events where no CRT-D device program modifications, no new cardiovascular drug administration or dose modification, and no subsequent therapy or cardiovascular hospitalization were performed (**Figure 4.**).

4.2.5. 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 (cardiovascular mortality) 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 $p < 0.05$.

4.3. Results

4.3.1. Patient populations

Total of 88 CRT-D recipients were included in the study. Patient baseline characteristics are summarized in **Table 5.** Despite patients being non-randomized in this study, RM and CFU patient groups did not differ significantly in most baseline features. There were

no significant differences regarding patient age (59.7 vs. 69.6; p = 0.2), female gender (12 vs. 7; p = 0.23), baseline left ventricular ejection fraction (29.49 vs. 30.27; p = 0.47), New York Heart Association (NYHA) functional class (2.82 vs. 2.88; p = 0.202), or number of patients with left bundle branch block (LBBB) morphology (42 vs. 40; p = 0.95) at the time of device implantation. The 2 patient populations showed no significant differences with respect to anamnestic cardiovascular comorbidities, number of ischemic cardiomyopathies (25 vs. 25; p = 0.86), paroxysmal or permanent atrial fibrillations (11 vs. 11; p = 0.9), chronic obstructive pulmonary disease (9 vs. 9; p = 0.499), chronic kidney disease (CKD) stage 3 defined as glomerular filtration ratio (GFR) between 60 ml/min and 30 ml/min (2 vs. 3; p = 0.673). Patients with a GFR below 30 ml/min were not included in this study. No significant differences were seen at baseline cardiovascular medical regime except for higher statin usage in the RM group (23 vs. 13; p = 0.008), no difference in point of baseline heart failure medication like ACE inhibitor/angiotensin receptor inhibitor (37 vs. 37; p = 0.59), b receptor blocker (41 vs. 39; p = 1.0), mineralocorticoid receptor antagonist (31 vs. 24; p = 0.31), diuretics (40 vs. 39; p = 1.0), and amiodarone (14 vs. 9; p = 0.377) usage. Anticoagulant (20 vs. 26; p = 0.12) and antiplatelet agent usage (22 vs. 20; p = 0.991) were also comparable at baseline in the RM and CFU groups.

Table 5. 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

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**

4.3.2. 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. Notably, post hoc power analysis with a 2-sided α of 5% and a statistical power of 88% was obtained for CV survival outcome. 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. Other clinically relevant factors like female sex, ischemic heart failure etiology, baseline left ventricular ejection fraction, relevant cardiovascular comorbidities, ventricular shock events, unscheduled ambulatory visit events, baseline medical regime, or even remote monitoring follow-up method were not independent predictors of CV mortality in our patient cohorts (**Figure 6.**). Although cardiovascular hospitalizations (37 vs. 46; p = 0.076) or the number of in-hospital spent days did not differ significantly (245 vs. 346; p = 0.35), 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). Echocardiographic control for evaluation of left ventricular function was reassessed 6-12 months after device implantation. No differences were seen in control of left ventricular ejection fraction between the 2 observed groups (33.1% vs. 32.2%; p = 0.91) (**Table 6.**).

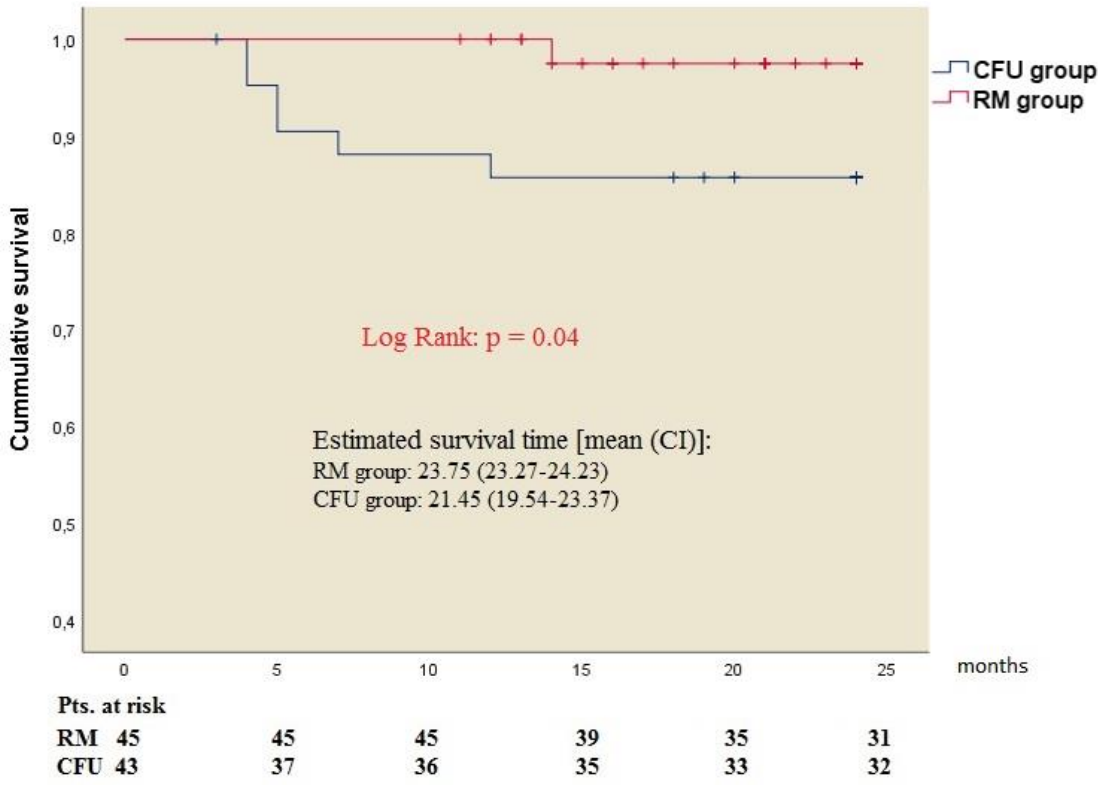

Figure 5. Kaplan-Meier's curve for estimated cardiovascular mortality in patient groups

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

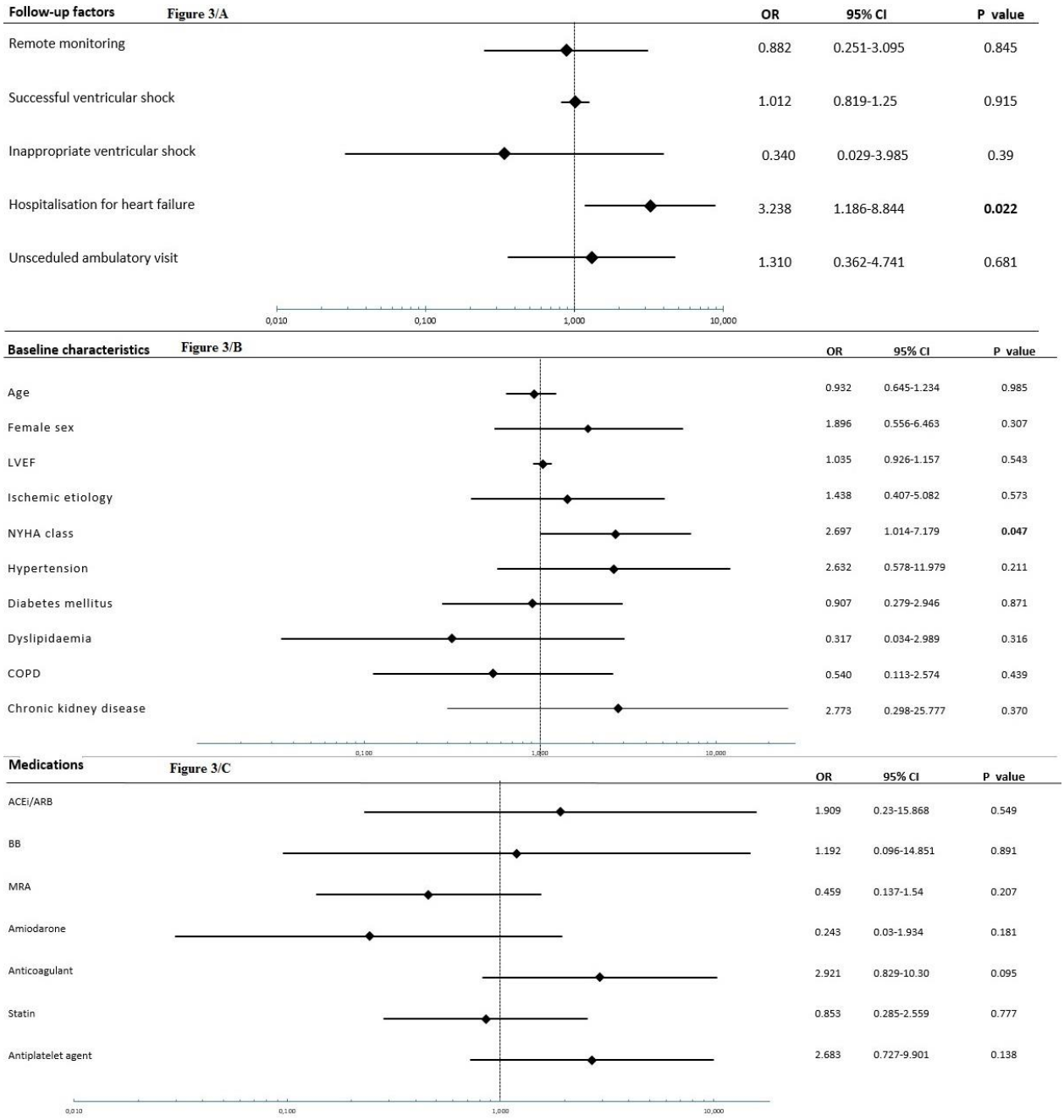

Figure 6. Variable regression analysis for predictors of mortality in 3 parameter groups (follow-up parameters (A), baseline characteristics (B), medications (C)).

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.

4.3.3. 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.**).
Comparable results were seen between the 2 groups regarding incidence of ventricular arrhythmias (243 vs. 205; p = 0.067) or ICD therapeutic response to arrhythmia (anti-tachycardia pacing (114 vs. 81; p = 0.876), appropriate ventricular shocks (50 vs. 44; p = 0.23)) respectively; even the count of inappropriate ventricular shocks (11 vs. 13; p = 0.83) or patient number affected by inappropriate shocks (4 vs. 3; p = 0.74) did not differ markedly (**Table 6.**).

Table 6. Follow-up related results.

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

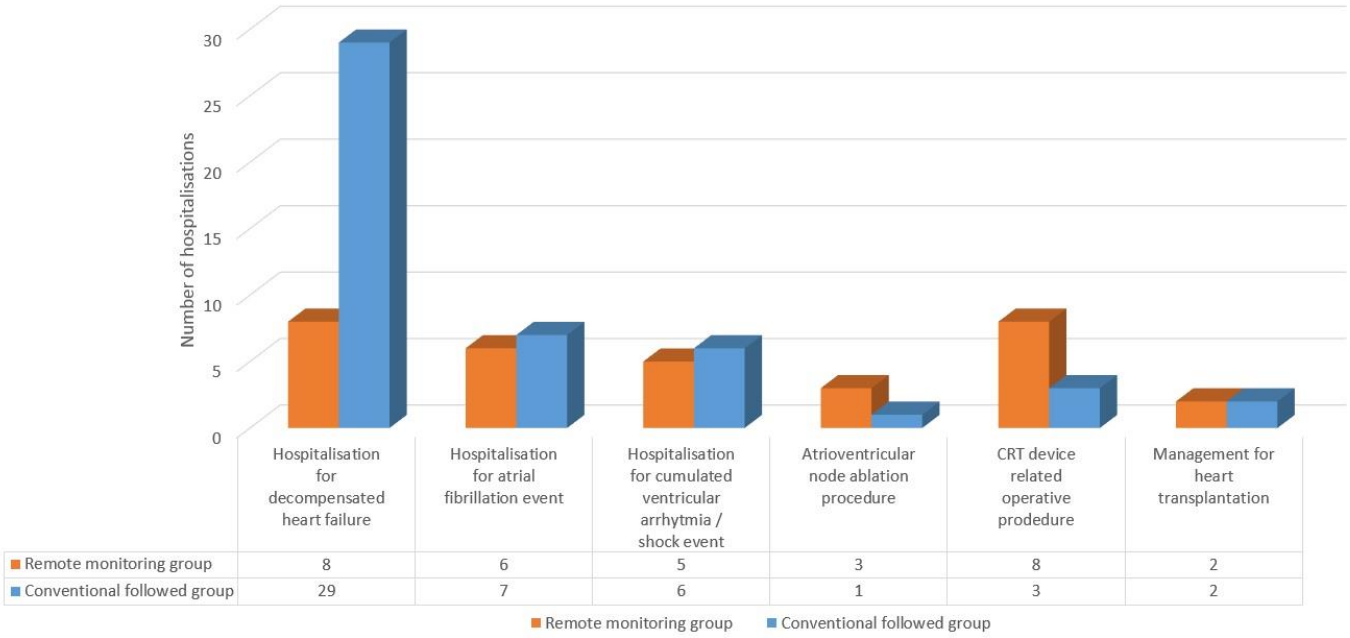

Figure 7. Distribution of cardiovascular hospitalization events during follow-up.

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.

4.3.4. 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. During a 2-year follow-up period, there were significantly fewer (as much as 39% lower) total ambulatory in-office visits (161 vs. 263; $p < 0.01$) in the RM group as compared to the CFU group. A numerically higher number was observable with respect to unscheduled ambulatory visit events in RM group (36 vs. 22; $p = 0.167$), but this difference was not statistically significant. The number of unscheduled unnecessary ambulatory visits was significantly lower in the RM group (6 vs. 19; $p = 0.012$). **Figure 8.** shows the improved efficacy of ambulatory patient flow in the remote monitoring group. In the RM arm, of those 30 unscheduled necessary ambulatory visits, 27 in-office patient evaluations were arranged because of worsening heart failure alert positivity seen during remote transmissions using our institutional algorithm. Twenty of 27 patients required higher diuretic

dose because of circulatory congestion and/or meaningful decrease in thoracic impedance value, but only 8 patients required hospitalization for decompensated heart failure, severe dyspnea, cardio-respiratory failure, or severe congestion signs. Eighteen patients required further cardiovascular medication modification, and only 4 required significant CRT device program modifications in ambulatory settings. Six patients had novel atrial fibrillation burden exceeding 6 hours with rapid ventricular rate and low biventricular pacing ratio. All the 6 patients required hospitalization, and 3 patients required further hospitalization for atrioventricular node ablation procedure as a consequence of medically refractory high ventricular rate atrial fibrillation. All patients required hospitalization with major ventricular sustained arrhythmia and > 1 inappropriate/appropriate ventricular shocks.

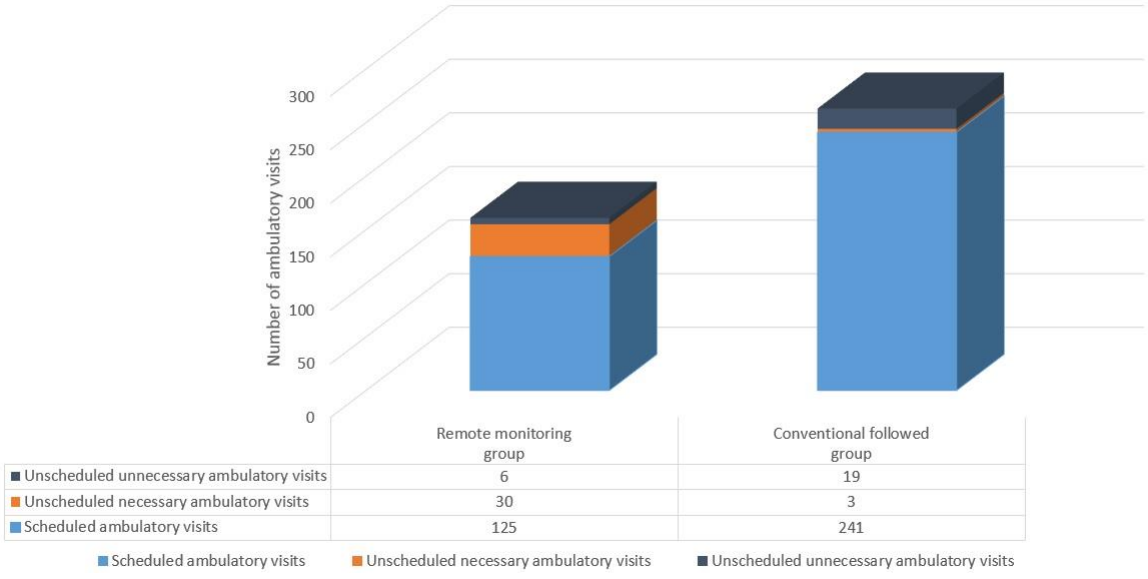

Figure 8. Ambulatory follow-up burden in the patient cohorts.

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.

4.3. 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 [25]. Implant-based automatic daily multi-parameter tele-monitoring of CIED patients with heart failure (IN-TIME study) first showed survival benefit in the remote monitoring arm in a patient group consisting of dual-chamber ICD- or CRT-D-implanted patients. The RM system transmitted data on daily basis; thus, the opportunity for closer heart failure status monitoring and management was given as compared to conventional care. The RM was associated with a 60% relative decrease in 1-year CV mortality in the IN-TIME trial; however, the RM group and the control group did not differ significantly for the number of hospital admissions for worsening heart failure [21].

In a recent meta-analysis by Klersy et al., RM follow-up failed to show a decrease in the total number of cardiovascular hospitalizations, but RM was associated with a reduction in total ambulatory visit count [58].

In another meta-analysis, Parthiban et al. demonstrated comparable all-cause mortality, cardiovascular mortality, and hospitalization outcomes in ICD patients with RM or conventional follow-up. However, a decrease in all-cause mortality was observed in those trials using RM systems with daily data transmission [26]. The latest meta-analysis consisting of 3 large trials (TRUST, ECOST, IN-TIME) all with automated daily transmission-based remote monitoring in heart failure CIED patients showed a reduced composite endpoint of worsening heart failure hospitalizations and cardiovascular death; however, unscheduled in-office visit numbers were not lower in the RM-followed group [27]. None of the above-mentioned trials 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.

Nowadays, in spite of advanced multi-parameter RM techniques, evidence is still lacking regarding optimization of early detection and fast intervention of CIED patients with higher risk of an impending heart failure event, but previous literature has applicable data on several monitored parameters.

Modern devices capable of measuring the patient's intrathoracic fluid status accelerate the early detection of patients with impending decompensated heart failure status. Thoracic impedance value change is the most widely studied factor, but evidence is lacking regarding optimal intervention thresholds for different device manufacturers. Intrathoracic fluid status is measured continuously by the implanted device in the form of intrathoracic impedance. As intrathoracic fluid accumulates, the intrathoracic impedance value decreases [8, 11, 63-65]. Although the predictive value of this parameter is well established in the literature, a single heart failure parameter alone seems to be too weak in daily practice to enable early and effective clinical intervention. PARTNERS-HF [12] and modified PARTNERS-HF criteria [13] both use a multi-parameter monitoring algorithm with monthly review to define patients with higher risk for heart failure decompensation. In these studies, a decrease in thoracic impedance value defines a higher risk patient group for an upcoming heart failure event. Furthermore, additional lower patient activity level, increased nocturnal ventricular heart rate, and suboptimal biventricular pacing ratio seemed to be the best independent predictors for heart failure events in patients with elevated intrathoracic fluid status [13].

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. Major predictors were sustained ventricular arrhythmia and ventricular shock events. More than one ventricular arrhythmia and/or ventricular shock event independently and strongly affected patient survival of advanced systolic heart failure patients with ICD; thus, urgent unscheduled in-office patient evaluation seems substantial in this clinical situation [66, 67]. New-onset atrial fibrillation burden exceeding 6 hours and higher ventricular rate are often the cause of lower biventricular pace ratio, functional worsening, and deterioration of heart failure status in CRT implanted patients [21]. Minor detection criteria prediction thresholds were optimized to have adequate

sensitivity for the detection of impeding decompensation events. In the case of at least 2 minor criteria positivity and fast consultation and interrogation of even minor patient complaints seemed to improve the ability for pre-emptive adequate HF therapy in these patients. Minor criteria like elevated resting ventricular heart rate and sudden decrease in heart rate variability are important markers of autonomic response in advanced heart failure, and both parameters correlate with worse clinical outcomes, increased count of heart failure events, and cardiovascular death [68-70]. According to current guidelines for cardiac resynchronization therapy, the biventricular pacing ratio of patients should be optimally as close to 100% as possible. Markedly decreased biventricular pacing ratio (e.g., < 80% for 48 hours in IN-TIME study) was one of the main findings for an upcoming heart failure event in different trials [21, 13, 71]. It should be noted that besides well-defined parameter thresholds in the case of decreased patient activity, heart rate variability, and increased resting ventricular heart rate, it is almost impossible to define the exact intervention threshold, and a patient-individualized clinical decision should be proposed.

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. Several national and international studies have dealt with the cost-effectiveness of remote monitoring. These studies revealed a significant reduction in costs for the health care system, primarily via the reduction in the costs of institutional ambulatory burden and in-office care services [3, 59-62]. As seen in the MORE CARE study [25], during a median 25-month follow-up, a clearly significant 41% decrease in expected ambulatory patient flow was observable at the health care institution, and the RM group had a significantly higher number of unscheduled ambulatory in-office patient evaluations. In spite of the above findings, 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.

We should note that RM requires good patient adherence to follow-up and therapy. Improving adherence in this patient group is important to improve clinical outcomes and quality of life [72]. COVID-19 (corona virus disease 2019) accelerated the need for eligible heart failure patient monitoring systems for patients with or without a cardiac implanted device. Achieving appropriate social distancing during lockdowns but still the possibility for close heart failure monitoring became essential for these patients. Tele-monitoring and "virtual visit" events have gained in importance in the last months of the pandemic. Several HF management-guiding principles have been recommended from experts in the field recently [40, 41]. Remote monitoring-mediated follow-up became more prominent in the last few months, and it will potentially play a valuable role in the follow-up of advanced heart failure CIED patients in the near future.

There are some limitations to address in our pilot study. Our 2 patient cohorts were selected retrospectively from our single university institute center in Hungary. Patient cohorts consisted of 45 vs. 43 patients, and further patient enrolment to increase the sample size and statistical power was limited. However, it should be emphasized that post hoc power analysis of the primary outcome revealed 88% power and for secondary endpoint outcome – 99% with a 5% value of α.

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.

In 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.

4.5. Funding

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

5.1. 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. Furthermore, even healthcare workers were prone to persistently increasing viral transmission rate affecting up to 29% of all active workers in this field in Italy [73].

Remote monitoring (RM) has revolutionized the follow-up of cardiac implantable electronic device (CIED) patients in the last 20 years. Prespecified device alerts - depending on the manufacturer of the system - provide support to follow certain physiological parameters, alert device malfunction, arrhythmia events and even deterioration in the patient's heart failure status reliably. This mode of detection promotes rapid response for urgent clinical and device technical issues thus leading to improved patient outcomes [20, 74]. Some studies of automated daily remote monitored advanced heart failure CIED patients resulted even in improved survival compared to conventional – IPE based – care [21, 27].

Detecting worsening heart failure remains one of the main trending issues in remote patient monitoring, although previously an upgraded remote patient monitoring based heart failure detection algorithm was published by Whellan et al. in PARTNERS HF trial [12] and was optimized by Vámos et al. [13]. This alert-based follow-up algorithm seems accurate enough to predict an upcoming heart failure event with sensitivity about 86.5% and specificity of 93%.

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 [39, 40] 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 [39, 41, 42, 43]. Some authors suggested consequent activation of RM function in all newly implanted CIEDs [44], or declared RM as essential in the follow-up of CIED patients during the pandemic [45, 46].
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.

5.2. Materials and Methods

Data were retrospectively acquisited 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 [49]. 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.

5.2.1Prespecified 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.

Detection alerts were inspired from previous PARTNERS HF study [12] and optimized on previous findings and clinical experience [13, 75].

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.

Recent decrease in thoracic impedance value or increase (60 Ohms <) in Optivol™ value, decrease in heart rate variability, patient activity level, increasing resting heart rate, sustained ventricular and supraventricular arrhythmia events and decrease in biventricular pacing ratio in resynchronization devices served as additive information about heart failure status in RMG.

In case of at least one major (sustained ventricular arrhythmia, anti-tachycardia therapy, new onset-, high ventricular rate atrial fibrillation events >6 hours a day) or in case of at least two minor alert positivity any potential patient symptoms were directly interrogated by a telephone contact and further heart failure related complaints were assessed.

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.

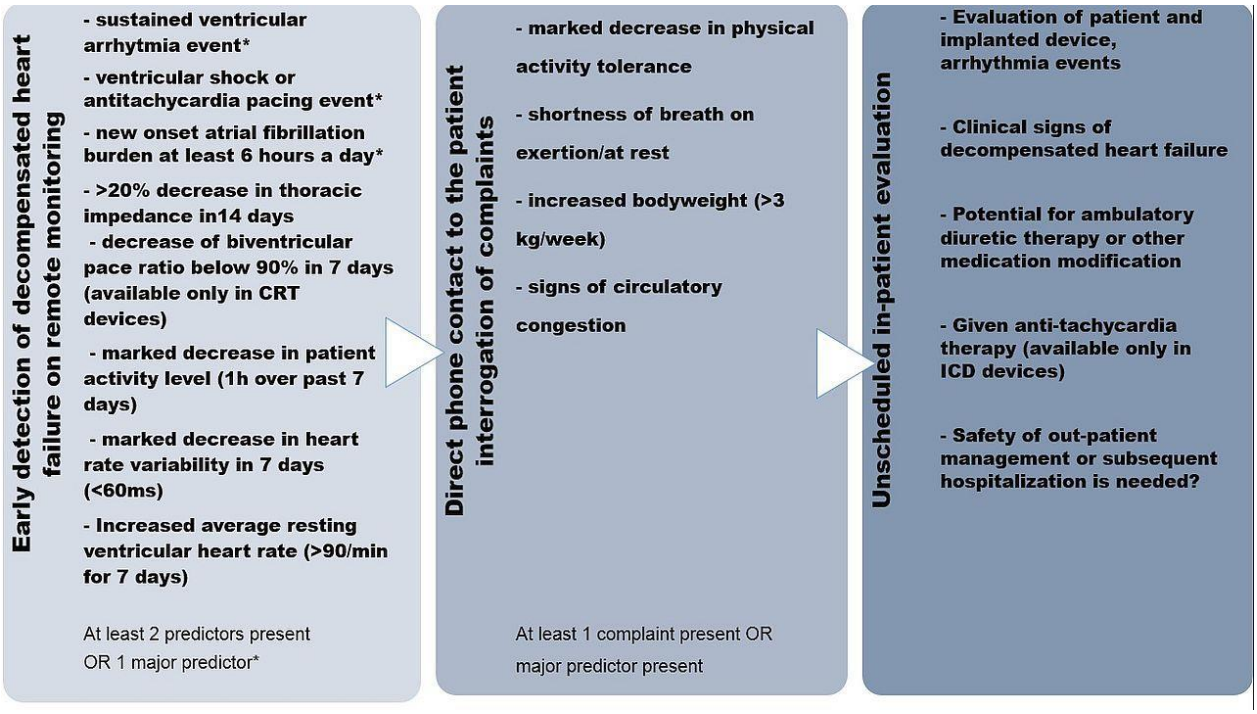

Figure 9. Preemptive detection of worsening heart failure related adverse events with the help of a predefined alert-based workflow. Major criteria in the alert-based detection algorithm were sustained ventricular arrhythmia or ventricular shock event, anti-tachycardia pacing event or new onset atrial 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.

5.2.2. Adverse event definitions

Sustained ventricular and/or supraventricular arrhythmia (ventricular tachycardia, fibrillation, atrial fibrillation) events requiring further treatment or appropriate/inappropriate ventricular shock events, new-onset- IPE or hospitalization necessitating arrhythmias were collected as arrhythmic adverse events in both patient groups.

Multiple alert signs of potential device dysfunction (abruptly elevated pacing threshold, out of range pacing- or shock impedance value, low battery status, over/undersensing etc.) were monitored continuously and marked as device related adverse events.

Even nowadays the definition of worsening heart failure (WHF) event is not universally accepted [76] and this definition bias can lead consequentially to improper event assessment, so we defined worsening heart failure event as at least one grade deterioration in New York Heart

Association heart failure functional class (NYHA class) from baseline and further need of parenteral diuretic- and other medical therapy intensification because of heart failure symptoms.

5.2.3. 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 $p < 0.05$.

5.3. Results

5.3.1. 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 or **Table 7**.

Table 7. Baseline patient parameters

	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**

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

5.3.2.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 8**. 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).

5.3.3. 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 8.**)

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.**

Table 8. Event rates in patient groups at 6 and 12 months of follow up

	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

Abbreviations: COVID-19: corona virus disease 2019, RMG: remote monitoring group, CFG: conventionally followed group.

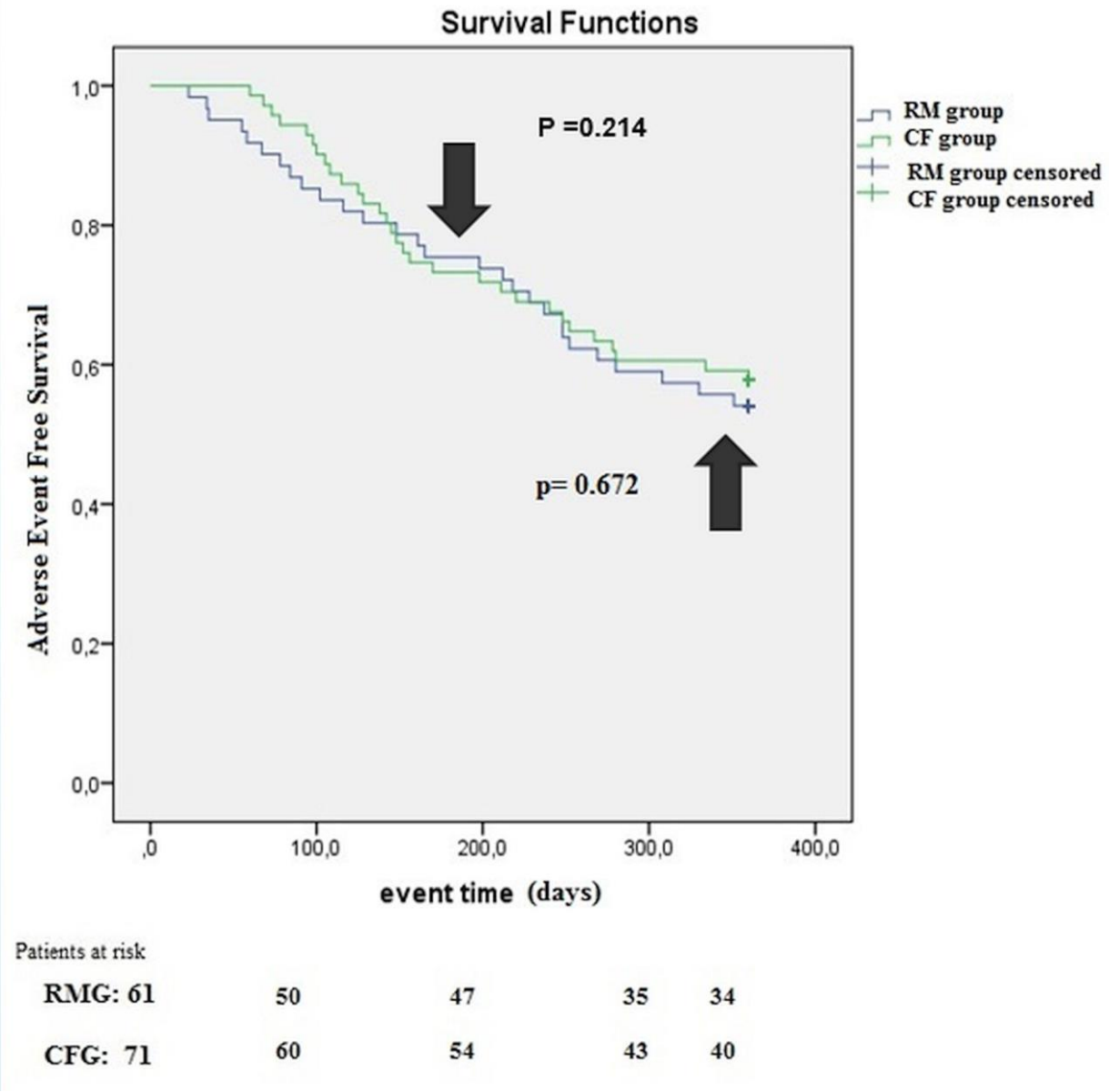

Figure 10. Kaplan-Meier's curve: Adverse event-free survival. The composite end-point of device-, arrhythmia and worsening heart failure related adverse event-free survival is statistically non-differing in the two observed patient groups neither at 180 days (log rank p=0.214) nor at 360 days (log rank p=0.672) of follow-up during the COVID-19 pandemic.

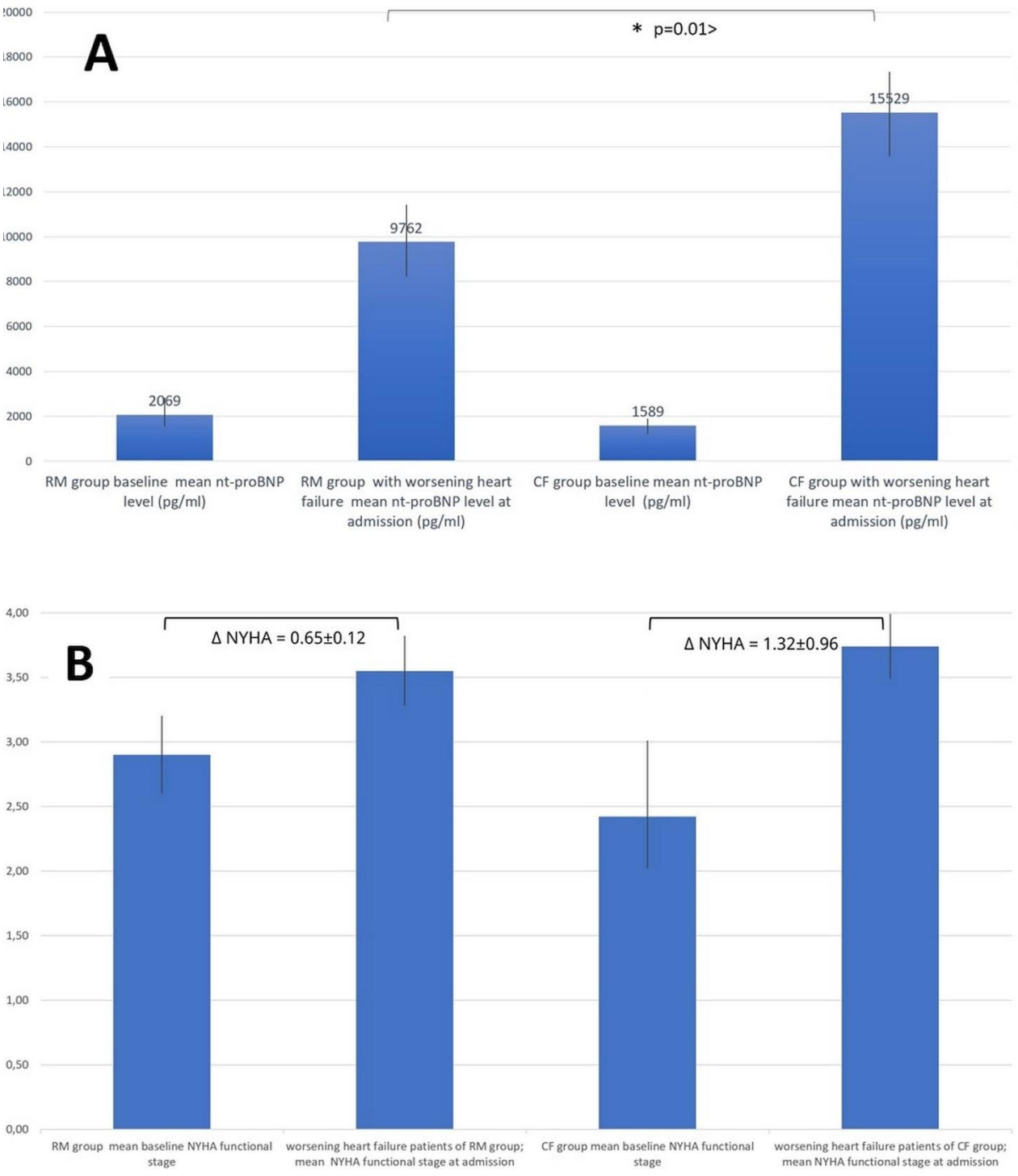

Figure 11. Comparison of NT-proBNP levels (A) and change in NYHA functional class (B) at baseline and hospital admissions for worsening heart failure in the remote monitoring (RMG) and conventionally followed (CFG) patient groups. Patients in the conventionally followed group (CFG) had a significantly increased N

terminal-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).

5.3.4.Correlational analysis

Spearman's rho correlational analysis and binary logistic regression analysis showed statistical correlation for worsening heart failure events in patients with permanent atrial fibrillation (p=0.025), higher baseline NYHA functional class (p=0.037), decreased left ventricular ejection fraction (p<0.001), increased left ventricular end-diastolic (p<0.01) and end-systolic (p<0.01) diameters.

Patients with permanent atrial fibrillation (p=0.018), increased left ventricular end-diastolic (p<0.01) and end-systolic diameters (p<0.01) and decreased left ventricular ejection fraction (p<0.01) had independently higher risk for hospitalization for worsening heart failure.

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.

5.4. 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 [12, 13, 75]. 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.

Recently D'Onofrio et al. introduced a validated multiparameter monitoring based prediction algorithm for heart failure hospitalizations in SELENE HF (Selection of potential predictors of worsening heart failure) trial [16]. A baseline risk-stratifier Seattle HF Model was combined with temporal trend of various physiological (diurnal- and nocturnal heart rate, heart rate variability, physical activity) arrhythmia (ventricular extrasystoles, atrial fibrillation burden) and thoracic

impedance parameters. Reaching the nominal index threshold of the algorithm, patients had substantially increased risk for heart failure hospitalization. The algorithm was showed to have an 65.5% sensitivity for an upcoming heart failure event with acceptable false/unexplained alert rate of 0.69 alert/patient/year.

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. [77] 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.

5.5. 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.

5.6. Funding

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6. Summary of the new scientific results

6.1. 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.

6.2. 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:

- Lesser 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 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.

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9.Publications of the author

9.1. Topic related journal articles

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Quartile: Q1 Impact factor: 2.73 (2020)

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9.2.Other articles

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9.3. Published abstracts, congress presentations and posters

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Automatic daily remote monitoring in heart failure patients implanted with a cardiac resynchronisation therapy-defibrillator: a single-centre observational pilot study

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Abstract

Introduction: The impact of remote monitoring (RM) on clinical outcomes in heart failure (HF) patients with cardiac resynchronisation therapy-defibrillator (CRT-D) implantation is controversial. This study sought to evaluate the performance of an RM follow-up protocol using modified criteria of the PARTNERS HF trial in comparison with a conventional follow-up scheme.
Material and methods: We compared cardiovascular (CV) mortality (primary endpoint) and hospitalisation events for decompensated HF, and the number of ambulatory in-office visits (secondary endpoint) in CRT-D implanted patients with automatic RM utilising daily transmissions (RM group, $n = 45$) and conventional follow-up (CFU group, $n = 43$) in a single-centre observational study.
Results: After a median follow-up of 25 months, a significant advantage was seen in the RM group in terms of CV mortality (1 vs. 6 death event, $p = 0.04$), although RM follow-up was not an independent predictor for CV mortality (HR = 0.882; 95% CI: 0.25–3.09; $p = 0.845$). Patient CV mortality was independently influenced by hospitalisation events for decompensated HF (HR = 3.24; 95% CI: 8–84; $p = 0.022$) during follow-up. We observed significantly fewer hospitalisation events for decompensated HF (8 vs. 29 events, $p = 0.046$) in the RM group. Furthermore, a decreased number of total (161 vs. 263, $p < 0.01$) and unnecessary ambulatory in-office visits (6 vs.19, $p = 0.012$) were seen in the RM group as compared to the CFU group.
Conclusions: Follow-up of CRT-D patients using automatic RM with daily transmissions based on modified PARTNERS HF criteria enabled more effective ambulatory interventions leading indirectly to improved CV survival. Moreover, RM directly decreased the number of HF hospitalizations and ambulatory follow-up burden compared to CRT-D patients with conventional follow-up.

Key words: survival, follow-up, heart failure, cardiac resynchronisation therapy, remote monitoring.

Introduction

Cardiac resynchronisation therapy (CRT) provides an evidence-level treatment manner in a well selected subgroup of patients with advanced systolic heart failure and functional dyssynchrony. Cardiac resynchronisa-

tion therapy is a proven method to reduce symptoms, morbidity (hospitalisations), and mortality in heart failure patients responding or super-responding to therapy [1, 2]. Remote monitoring of patients with cardiac implantable devices (CIED) in heart failure has an established recommendation according to the currently available heart failure guidelines of the European Society of Cardiology (ESC) [3]. Cardiac resynchronisation therapy-defibrillators (CRT-D), capable of remote monitoring (RM) function, transmit numerous measurable patient- and device-related data on a predetermined time basis or even immediately if a critical event is observed by the implanted device. Detection alerts and transmission algorithms depend on the manufacturer of the system.

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) [4–8]. 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 [7–10].

The PARTNERS HF study investigated 694 CRT defibrillator patients with remote monitoring and continuous multi-parameter monitoring for heart failure. Monthly review of monitored parameters and patients with positive combined heart failure diagnostics of long-lasting atrial fibrillation and/or high ventricular rate, low biventricular pacing ratio, abnormal autonomic signs (elevated resting heart rate, low heart rate variability), decreased patient activity, and high thoracic fluid index had a 5.5-fold increase in the risk for heart failure hospitalisations within the subsequent month. Evaluation of heart failure device diagnostics more frequent than one week improved the ability to risk stratify patients for subsequent heart failure events [11].

Although previous result are well proven, the exact alerting thresholds for each detection parameter are still debated, and a novel heart failure detection algorithm and effective intervention are highly warranted to prevent worsening heart failure-related hospitalisation and death.

Remote monitored heart failure patients implanted with cardiac implantable devices (CIEDS) show contradicting outcome results regarding survival, hospitalisation, and institutional ambulatory burden in prospective randomised studies and meta-analyses [12–16].

Nevertheless, several trials proved an equivocal decrease in institutional ambulatory burden and cost effectiveness in the care of remote monitored patients [17–22].

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 hospitalisations and increase survival compared to a conventional 'ambulatory-only'-followed patient group, without increasing hospital ambulatory burden or the number of unscheduled in-office patient evaluations in an RM-followed patient group of CRT-D-implanted patients.

Material and methods

Study design

This investigation was a single-centre 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 [3]. 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. The opportunity for remote monitoring and device remote follow-up was offered to every patient before implantation if an RM eligible Iforia device and Cardiomessenger device were available at the same time. Remote transmission device availability was the main selection criterion, whether a patient was followed with remote monitoring or not.

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-randomised 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). Biotronik devices with a Home Monitoring remote monitoring system were chosen for the retrospective analysis because the system provides daily transmission based automatic remote monitoring, and the specific device was

the most available in our institute at the time of device implantations.

Follow-up data of 88 *de novo* CRT-D-implanted patients were collected and analysed. 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. Table I presents the parameters that were assessed at remote interrogation and/or in-office ambulatory follow-up events.

Data regarding CV mortality, cardiovascular hospitalisations, institutional admissions for decompensated heart failure, ambulatory patient flow, baseline characteristics, medications, and comorbidities were collected from patient files, remote interrogations of the device, and from an integrated patient care information system of University of Pécs. 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).

Study endpoints

The primary objective of this study was to compare the CV mortality of remote-monitored patients with patients on a conventional follow-up scheme. Survival was assessed as the time from CRT-D implantation to a CV mortality event. Secondary endpoints were the number of cardiovascular hospitalisations, expressively the number of hospitalisations for decompensated heart failure. Further secondary endpoints were the total number of ambulatory visits, and the ratio of unnecessary ambulatory visits in each patient group during follow-up.

Novel detection algorithm for worsening heart failure in the 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-centre observational study [11] 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. Vamos *et al*. [23] 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

Table I. Parameters assessed at remote interrogation and in-office follow-up

Parameter type	
Current rhythm diagnosis and pacemaker dependency	Therapy given for sustained ventricular arrhythmia (anti-tachycardia pacing, ventricular shock)*
Mean ventricular heart rate*	Biventricular pacing ratio*
Battery lifetime expectancy	Inappropriate ventricular shock events*
Lead impedance/shock lead impedances	Review of device-triggered alert events*
Pacing thresholds for different electrodes	Patient activity level*
Sensing signal amplitude threshold for different electrodes	Heart rate variability*
All arrhythmia events (atrial arrhythmia burden, ventricular extrasystoles, and other arrhythmia events)*	Intrathoracic impedance status*

**Parameters influencing heart failure status management.*

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 II 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 hospitalisation for decompensated heart failure. Our institutional criteria-protocol for screening remote monitored patients with impeding status for decompensated heart failure is shown in Figure 1.

Ambulatory visit definitions

Patient flow at our institute was assessed with respect to all ambulatory visits in both patient groups, divided into scheduled, unscheduled necessary, and unscheduled unnecessary ambulatory visit events. Scheduled ambulatory visits were always in the form of a prearranged ambulatory appointment at least once a year in the RM group and every 3 to 6 months in the CFU group. Unscheduled ambulatory in-office visits only occurred in the RM group if at least 1 major RM criteria for heart failure or at least 2 minor criteria with even modest heart failure symptoms at patient interrogation occurred. These patients were urgently contacted, and a pre-emptive unscheduled ambulatory visit was arranged. Patients in the CFU group were checked at scheduled visits; unscheduled visits were only set up based on general physician referral, emergency physician referral, or severe patient complaints. Unscheduled ambulatory visits qualified as unnecessary in-office visits were visit events where no CRT-D device programme modifications, no new cardiovascular drug administration or dose modification, and no subsequent therapy or cardiovascular hospitalisation were performed (Figure 1).

Statistical analysis

All follow-up variables were divided to categorical or continuous variables. Data are presented as mean ± standard deviation for normally dis-

Table II. Comparison of refined PARTNERS HF [22] and remote monitoring criteria for predicting decompensated heart failure events in our institute

Device parameter	Refined PARTNERS HF criteria [22]	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 > 6 h on at least one day without persistent AF	New onset AF at least 6 h 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 without therapy

AF – atrial fibrillation.

tributed 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 (cardiovascular mortality) based on Kaplan-Meier survival analysis using Stata version 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College, TX: StataCorp LLC.). The level of significancy was defined as $p < 0.05$.

Results

Patient populations

Total of 88 CRT-D recipients were included in the study. Patient baseline characteristics are summarised in Table III. Despite patients being non-randomised in this study, RM and CFU patient groups did not differ significantly in most baseline features. There were no significant differences regarding patient age (59.7 vs. 69.6; $p = 0.2$), female gender (12 vs. 7; $p = 0.23$), baseline left ventricular ejection fraction (29.49 vs. 30.27; $p = 0.47$), New York Heart Association (NYHA) functional class (2.82 vs. 2.88; $p = 0.202$), or number of patients with left bundle branch block (LBBB) morphology (42 vs. 40; $p = 0.95$) at the time of device implantation. The 2 patient populations showed no significant differences with respect to anamnestic cardiovascular comorbidities, number of ischaemic cardiomyopathies (25 vs. 25; $p = 0.86$), paroxysmal or permanent atrial fibrillations (11 vs. 11; $p = 0.9$), chronic obstructive pulmonary disease (9 vs. 9; $p = 0.499$), chronic kidney disease (CKD) stage 3 defined as glomerular filtration ratio (GFR) between 60 ml/min and 30 ml/min (2 vs. 3; $p = 0.673$). Patients with a GFR below 30 ml/min were not included in this study. No significant differences were seen at baseline cardiovascular medical regime except for higher statin usage in the RM group (23 vs. 13; $p = 0.008$), no difference in point of baseline heart failure medication like ACE inhibitor/angiotensin receptor inhibitor (37 vs. 37; $p = 0.59$), β receptor blocker (41 vs. 39; $p = 1.0$), mineralocorticoid receptor antagonist (31 vs. 24; $p = 0.31$), diuretics (40 vs. 39; $p = 1.0$), and amiodarone (14 vs. 9; $p = 0.377$) usage. Anticoagulant (20 vs. 26; $p = 0.12$) and antiplatelet agent usage (22 vs. 20; $p = 0.991$) were also comparable at baseline in the RM and CFU groups.

Improved cardiovascular survival and less hospitalisation 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 2). The Kaplan-Meier estimate of 1-year CV mortality was 1.45% in the RM group and 6.92%

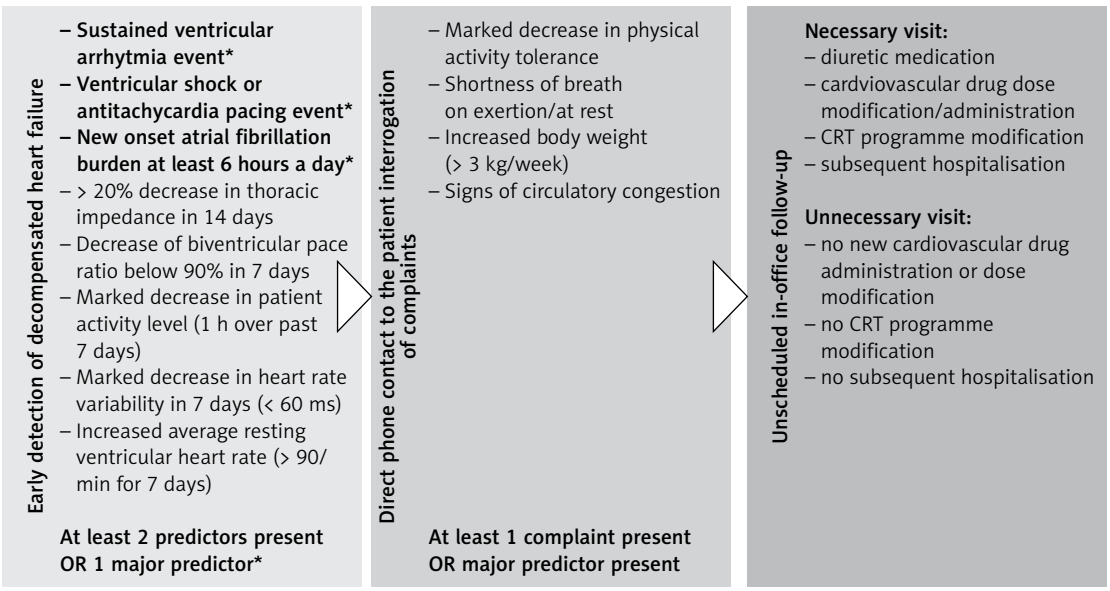


Figure 1. Institutional remote monitoring protocol for early detection of decompensated heart failure in cardiac resynchronisation therapy-defibrillator-implanted heart failure patients. Major predictors for impeding heart failure event were marked as *. At least two minor criteria positivity resulted in direct patient contact

Table III. Comparison of baseline patient characteristics

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)	0.950
Ischemic aetiology, *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
Hyperlipidaemia, *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			
β-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

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.

in the CFU group. Notably, post hoc power analysis with a 2-sided α of 5% and a statistical power of 88% was obtained for CV survival outcome.

Potential parameters for predicting CV mortality were divided into 3 parameter subgroups. Relevant patient baseline characteristics, follow-up parameters, and medication factors were analysed 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 hospitalisation 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. Other clinically relevant factors like female sex, ischaemic heart failure aetiology, baseline left ventricular ejection fraction, relevant cardiovascular comorbidities, ventricular shock events, unscheduled ambulatory visit events, baseline medical regime, or even remote monitoring follow-up method were not independent predictors of CV mortality in our patient cohorts (Figure 3).

Although cardiovascular hospitalisations (37 vs. 46; p = 0.076) or the number of in-hospital spent days did not differ significantly (245 vs. 346; p = 0.35), in terms of hospitalisation events for decompensated heart failure we noted a significant difference, with the RM group performing better (8 vs. 29; p = 0.046).

Echocardiographic control for evaluation of left ventricular function was reassessed 6-12 months after device implantation. No differences were

seen in control of left ventricular ejection fraction between the 2 observed groups (33.1 vs. 32.2; $p = 0.91$) (Table IV).

Hospitalisation, 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 haematoma evacuations were performed in the RM group, whereas 2 pacing electrode change/repositioning and 1 pocket haematoma evacuation in the CFU group were performed (Figure 4).

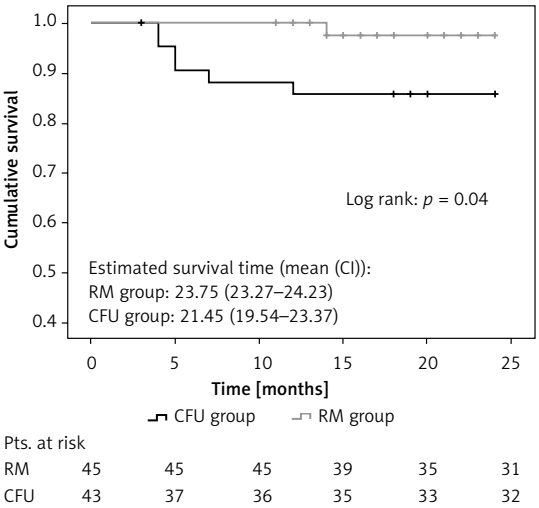
Comparable results were seen between the 2 groups regarding incidence of ventricular arrhythmias (243 vs. 205; $p = 0.067$) or ICD therapeutic response to arrhythmia (anti-tachycardia pacing (114 vs. 81; $p = 0.876$), appropriate ventricular shocks (100 vs. 88; $p = 0.23$)) respectively; even the count of inappropriate ventricular shocks (11 vs. 13; $p = 0.83$) or patient number affected by inappropriate shocks (4 vs. 3; $p = 0.74$) did not differ markedly (Table IV).

Effectivity of institutional ambulatory care

During median 30 months of follow-up 38,521 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. During a 2-year follow-up period, there were significantly fewer (as much as 39% lower) total ambulatory in-office visits (161 vs. 263; $p < 0.01$) in the RM group as compared to the CFU group. A numerically higher number was observable with respect to unscheduled ambulatory visit events in RM group (36 vs. 22; $p = 0.167$), but this difference was not statistically significant. The number of unscheduled unnecessary ambulatory visits was significantly lower in the RM group (6 vs. 19; $p = 0.012$). Figure 5 shows the improved efficacy of ambulatory patient flow in the remote monitoring group.

In the RM arm, of those 30 unscheduled necessary ambulatory visits, 27 in-office patient evaluations were arranged because of worsening heart failure alert positivity seen during remote transmissions using our institutional algorithm. Twenty of 27 patients required higher diuretic dose because of circulatory congestion and/or meaningful decrease in thoracic impedance value, but only 8 patients required hospitalisation for decompensated heart failure, severe dyspnoea, cardio-respiratory failure, or severe congestion signs.



Pts. at risk

RM	45	45	45	39	35	31
CFU	43	37	36	35	33	32

Figure 2. Kaplan-Meier estimation of cardiovascular mortality. 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

Eighteen patients required further cardiovascular medication modification, and only 4 required significant CRT device program modifications in ambulatory settings.

Six patients had novel atrial fibrillation burden exceeding 6 hours with rapid ventricular rate and low biventricular pacing ratio. All the 6 patients required hospitalisation, and 3 patients required further hospitalisation for atrioventricular node ablation procedure as a consequence of medically refractory high ventricular rate atrial fibrillation. All patients required hospitalisation with major ventricular sustained arrhythmia and > 1 inappropriate/appropriate ventricular shocks.

Discussion

This study sought to evaluate the impact of a novel remote monitoring heart failure detection algorithm, designed for an automated 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 hospitalisations and institutional ambulatory patient burden beneath more effective in-office patient care even in our pilot study with moderate patient cohorts.

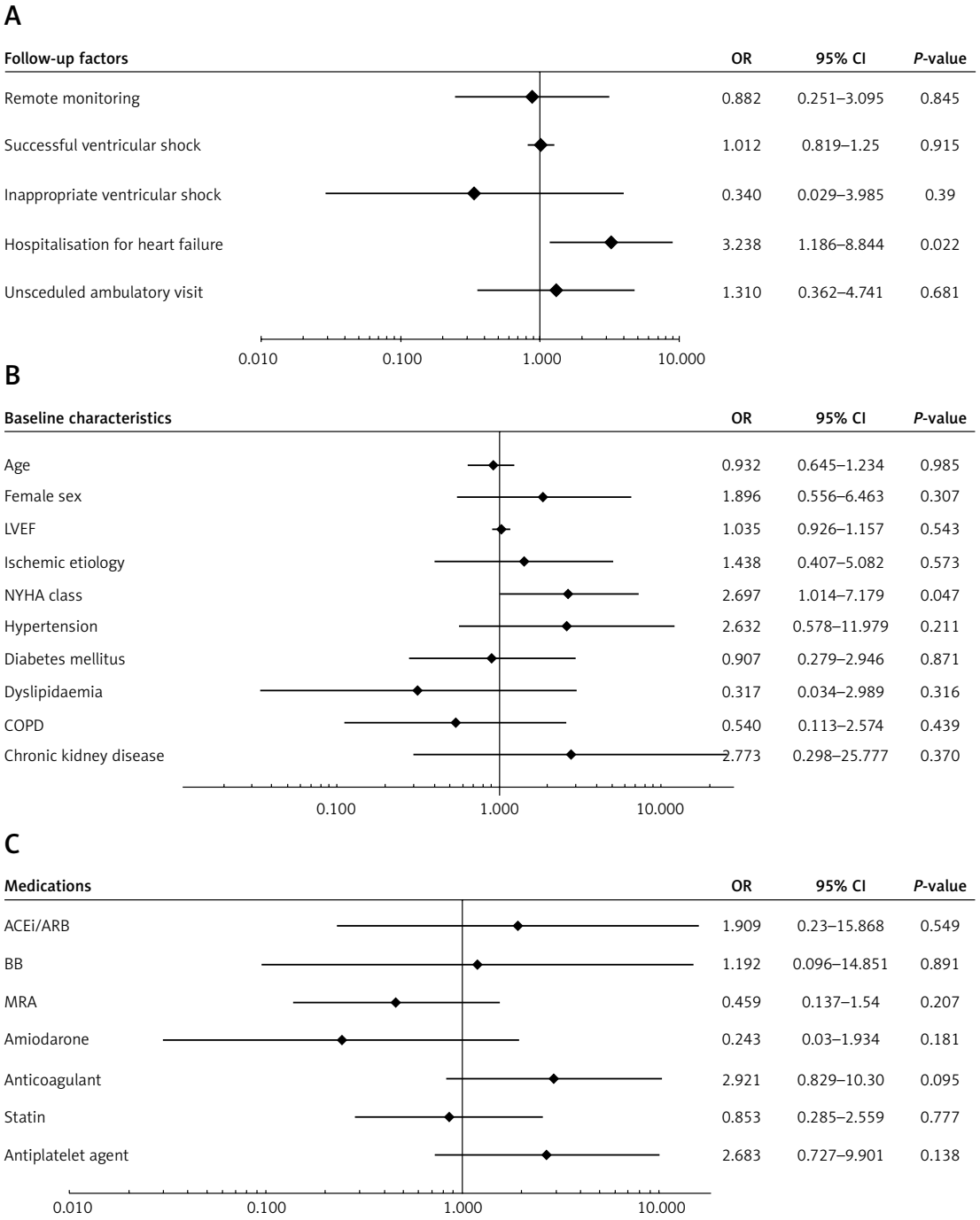


Figure 3. Variable regression analysis for predictors of mortality in 3 parameter groups (follow-up parameters (**A**), baseline characteristics (**B**), medications (**C**)). Analysis for cardiovascular mortality predictors was performed in 3 different parameter groups (A, B, C). New York Heart Association class ($p = 0.047$) and hospitalisation 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.

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 [14].

Implant-based automatic daily multi-parameter tele-monitoring of CIED patients with heart failure (IN-TIME study) first showed survival benefit in the remote monitoring arm in a patient group consisting of dual-chamber ICD- or CRT-D-implanted patients. The RM system transmitted data on

Table IV. Follow-up-related results

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 hospitalisation events, n	37	46	0.76
Days spent for cardiovascular hospitalisations, n	245	346	0.35
Hospitalisation 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
Sustained ventricular arrhythmias, n	243	205	0.067
Anti-tachycardia pacing events, n	114	81	0.876
Appropriate, successful ventricular shocks, n	100	88	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

daily basis; thus, the opportunity for closer heart failure status monitoring and management was given as compared to conventional care. The RM was associated with a 60% relative decrease in 1-year CV mortality in the IN-TIME trial; however, the RM group and the control group did not differ significantly for the number of hospital admissions for worsening heart failure [13].

In a recent meta-analysis by Klersy *et al*., RM follow-up failed to show a decrease in the total number of cardiovascular hospitalisations, but RM was associated with a reduction in total ambulatory visit count [15]. In another meta-analysis, Parthiban *et al*. demonstrated comparable all-cause mortality, cardiovascular mortality, and hospitalisation outcomes in ICD patients with RM or

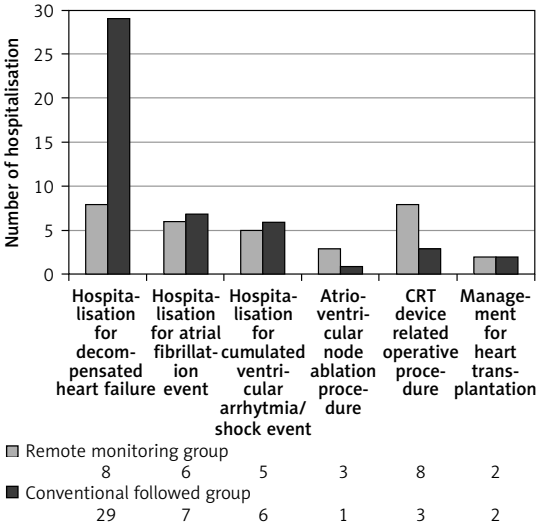


Figure 4. Distribution of cardiovascular hospitalisation events during follow-up. Higher number of hospitalisations for worsening heart failure is observable in the CFU group (8 vs. 29, p = 0.046). There were no significant differences regarding other cardiac or device-related hospitalisation events

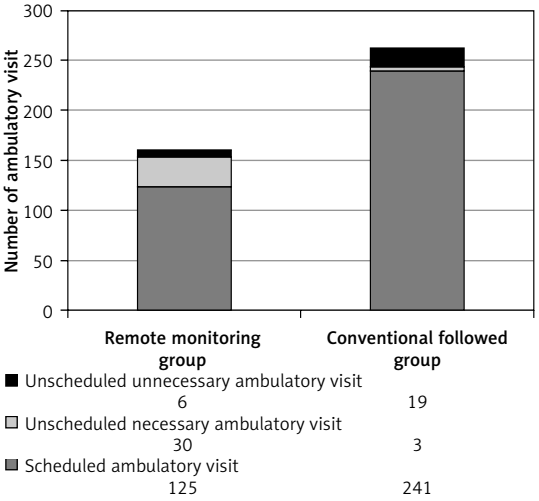


Figure 5. Ambulatory follow-up burden in the 2 patient cohorts. Ambulatory patient flow graph shows a total 39% (161 vs. 263) reduction of ambulatory admissions between the 2 patient groups (p < 0.01). A significantly lower (6 vs. 19; p = 0.012) number of unnecessary ambulatory patient admissions was also observed

conventional follow-up. However, a decrease in all-cause mortality was observed in those trials using RM systems with daily data transmission [16].

The latest meta-analysis consisting of 3 large trials (TRUST, ECOST, IN-TIME) all with automated daily transmission-based remote monitoring in heart failure CIED patients showed a reduced composite endpoint of worsening heart failure hospitalisations and cardiovascular death; however, unscheduled in-office visit numbers were not lower in the RM-followed group [25]. None of the above-mentioned trials and meta-analyses reported improved cardiovascular patient survival, decreased hospitalisation 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.

Nowadays, in spite of advanced multi-parameter RM techniques, evidence is still lacking regarding optimisation of early detection and fast intervention of CIED patients with higher risk of an impeding heart failure event, but previous literature has applicable data on several monitored parameters. Modern devices capable of measuring the patient's intrathoracic fluid status accelerate the early detection of patients with impending decompensated heart failure status. Thoracic impedance value change is the most widely studied factor, but evidence is lacking regarding optimal intervention thresholds for different device manufacturers. Intrathoracic fluid status is measured continuously by the implanted device in the form of intrathoracic impedance. As intrathoracic fluid accumulates, the intrathoracic impedance value decreases [25–29]. Although the predictive value of this parameter is well established in the literature, a single heart failure parameter alone seems to be too weak in daily practice to enable early and effective clinical intervention. PARTNERS HF [11] and modified PARTNERS HF criteria [23] both use a multi-parameter monitoring algorithm with monthly review to define patients with higher risk for heart failure decompensation. In these studies, a decrease in thoracic impedance value defines a higher risk patient group for an upcoming heart failure event. Furthermore, additional lower patient activity level, increased nocturnal ventricular heart rate, and suboptimal biventricular pacing ratio seemed to be the best independent predictors for heart failure events in patients with elevated intrathoracic fluid status [23]. 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.

Major predictors were sustained ventricular arrhythmia and ventricular shock events. More than one ventricular arrhythmia and/or ventricular shock event independently and strongly affected patient survival of advanced systolic heart failure patients with ICD; thus, urgent unscheduled in-office patient evaluation seems substantial in this clinical situation [30, 31]. New-onset atrial fibrillation burden exceeding 6 hours and higher ventricular rate are often the cause of lower biventricular pace ratio, functional worsening, and deterioration of heart failure status in CRT implanted patients [13].

Minor detection criteria prediction thresholds were optimised to have adequate sensitivity for the detection of impeding decompensation events. In the case of at least 2 minor criteria positivity and fast consultation and interrogation of even minor patient complaints seemed to improve the ability for pre-emptive adequate HF therapy in these patients. Minor criteria like elevated resting ventricular heart rate and sudden decrease in heart rate variability are important markers of autonomic response in advanced heart failure, and both parameters correlate with worse clinical outcomes, increased count of heart failure events, and cardiovascular death [32–34]. According to current guidelines for cardiac resynchronisation therapy, the biventricular pacing ratio of patients should be optimally as close to 100% as possible. Markedly decreased biventricular pacing ratio (e.g. < 80% for 48 hours in IN-TIME study) was one of the main findings for an upcoming heart failure event in different trials [13, 23, 35].

It should be noted that besides well-defined parameter thresholds in the case of decreased patient activity, heart rate variability, and increased resting ventricular heart rate, it is almost impossible to define the exact intervention threshold, and a patient-individualised clinical decision should be proposed.

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 hospitalisation 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.

Several national and international studies have dealt with the cost-effectiveness of remote monitoring. These studies revealed a significant reduction in costs for the health care system, primarily via the reduction in the costs of institutional ambulatory burden and in-office care services [18–22, 36]. As seen in the MORE CARE study [14], during a median 25-month follow-up, a clearly significant 41% decrease in expected ambulatory patient flow was observable at the health care institution, and the RM group had a significantly higher num-

ber of unscheduled ambulatory in-office patient evaluations. In spite of the above findings, 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 hospitalisation. These findings suggest that unscheduled unnecessary visits have been minimised 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.

We should note that RM requires good patient adherence to follow-up and therapy. Improving adherence in this patient group is important to improve clinical outcomes and quality of life [37].

COVID-19 (corona virus disease 2019) accelerated the need for eligible heart failure patient monitoring systems for patients with or without a cardiac implanted device. Achieving appropriate social distancing during lockdowns but still the possibility for close heart failure monitoring became essential for these patients. Tele-monitoring and "virtual visit" events have gained in importance in the last months of the pandemic. Several HF management-guiding principles have been recommended from experts in the field recently [38, 39]. Remote monitoring-mediated follow-up became more prominent in the last few months, and it will potentially play a valuable role in the follow-up of advanced heart failure CIED patients in the near future.

There are some limitations to address in our pilot study. Our 2 patient cohorts were selected retrospectively from our single university institute centre in Hungary. Patient cohorts consisted of 45 vs. 43 patients, and further patient enrolment to increase the sample size and statistical power was limited. However, it should be emphasised that *post hoc* power analysis of the primary outcome revealed 88% power and for secondary endpoint outcome – 99% with a 5% value of α. This investigation was a non-randomised 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.

In 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 hospitalisations 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 randomised trials with major patient populations are needed to confirm the results observed in our study.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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RESEARCH

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

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Abstract

Background: Coronavirus disease 2019 (COVID-19) had spread into a pandemic affecting healthcare providers worldwide. Heart failure patients with implanted cardiac devices require close follow-up in-spite of pandemic related healthcare restrictions.

Methods: Patients were retrospectively registered and clinical outcomes were compared of 61 remote monitored (RMG) versus 71 conventionally (in-office only) followed (CFG) cardiac device implanted, heart failure patients. Follow-up length was 12 months, during the COVID-19 pandemic related intermittent insitutional restrictions. We used a specified heart failure detection algorithm in RMG. This investigation compared worsening heart failure-, arrhythmia- and device related adverse events as primary outcome and heart failure hospitalization rates as secondary outcome in the two patient groups.

Results: No significant difference was observed in the primary composite end-point during the first 12 months of COVID-19 pandemic ($p = 0.672$).

In RMG, patients who had worsening heart failure event had relative modest deterioration in heart failure functional class ($p = 0.026$), relative lower elevation of N terminal-pro BNP levels ($p < 0.01$) at in-office evaluation and were less hospitalized for worsening heart failure in the first 6 months of pandemic ($p = 0.012$) compared to CFG patients.

Conclusions: Specified remote monitoring alert-based detection algorithm and workflow in device implanted heart failure patients may potentially indicate early worsening in heart failure status. Preemptive adequate intervention may prevent further progression of deteriorating heart failure and thus prevent heart failure hospitalizations.

Keywords: Heart failure, Remote monitoring, Follow-up, COVID-19

Background

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

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restrictions had limited the patients physical contact to the medical staff.

COVID-19 fundamentally altered healthcare logistics and patient access to healthcare services. Furthermore even healthcare workers were prone to persistently increasing viral transmission rate affecting up to 29% of all active workers in this field in Italy [1].

Remote monitoring (RM) has revolutionized the follow-up of cardiac implantable electronic device (CIED) patients in the last 20 years. Prespecified device alerts—depending on the manufacturer of the system—provide support to follow certain physiological parameters, alert device malfunction, arrhythmia events and even deterioration in the patients heart failure status reliably. This mode of detection promotes rapid response for urgent clinical and device technical issues thus leading to improved patient outcomes [2, 3]. Some studies of automated daily remote monitored advanced heart failure CIED patients resulted even in improved survival compared to conventional – IPE based – care [4, 5].

Detecting worsening heart failure remains one of the main trending issues in remote patient monitoring, although previously an upgraded remote patient monitoring based heart failure detection algorithm was published by Whellan et al. in PARTNERS HF trial [6] and was optimalized by Vámos et al. [7]. This alert based follow-up algorithm seems accurate enough to predict an upcoming heart failure event with sensitivity about 86.5% and specificity of 93%.

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 [8, 9] and expert position statements were published for reducing in-office patient evaluation follow-up burden and face-to-face visit events resulting in potential minimised exposure of patients and healthcare workers [8, 10–12]. Some authors suggested consequent activation of RM function in all newly implated CIEDs [13], or declared RM as essential in the follow-up of CIED patients during the pandemic [14, 15]. Aim of this study was to investigate, wheter 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 clinival adverse events compared to a conventionally followed (non-monitored) patient group during the special scenario of COVID-19 pandemic.

Methods

Data were retrospectively acquisited 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 consenus with currently available guidelines of European Society of Cardiology for device therapy and heart failure [16]. 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 studyprotocol 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

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.

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. Figure 1 shows specified remote monitoring detection algorithm and workflow in our institute for RPM capable CIED patients. Detection alerts were inspired from previous PARTNERS

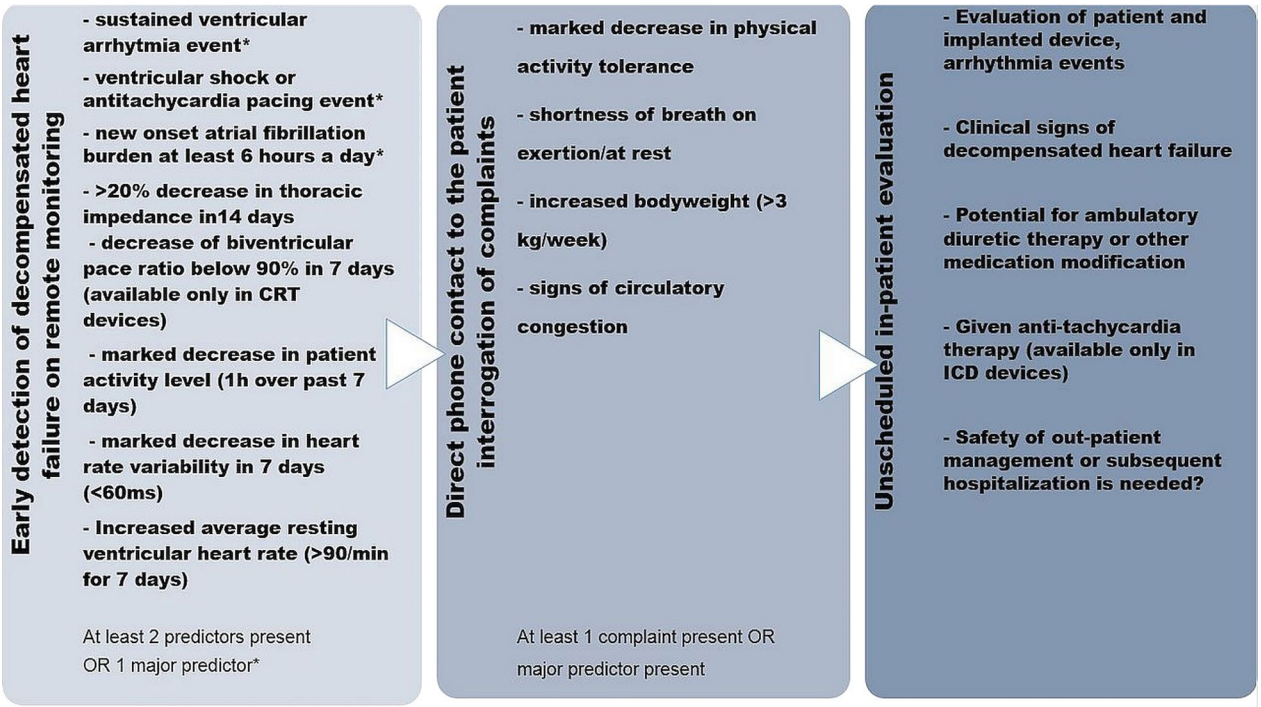

Fig. 1 Preemptive detection of worsening heart failure related adverse events with the help of a predefined alert based workflow. Major criteria in the alert based detection algorithm were sustained ventricular arrhythmia or ventricular shock event, anti-tachycardia pacing event or new onset atrial fibrillation burden exceeding 6 h 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

HF study [6] and optimalized on previous findings and clinical experience [7, 17].

Early detection of worsening heart failure was implemented by specific heart failure detection algorithms of Biotronik and Medtronic devices, general considerations are shown on Fig. 1. Monitoring data trends and alerting events were revised in weekly frequency.

Recent decrease in thoracic impendance value or increase (60 Ohms<) in Optivol™ value, decrease in heart rate variability, patient activity level, increasing resting heart rate, sustainded ventricular and supraventricular arrhthymia events and decrease in biventricular pacing ratio in resynchronization devices served as additive information about heart failure status in RMG.

In case of at least one major (sustained ventricular arrhtyhmia, anti-tachycardia therapy, new onset-, high ventricular rate atrial fibrillation events>6 h a day) or in case of at least two minor alert positivity any potential patient symptoms were directly interrogated by a telephone contact and further heart failure related complaints were assessed.

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 practinioner referral. In this cases IPEs were strongly complaint and symptom-based in this patient group.

Study endpoints

The objective in this study was to compare adverse event rates in primary composite end-point of sustained arrhythmia- device- and worsening heart failure related adverse events in the patient groups during 12 months of COVID-19 pandemic.

The secondary end-point was to assess rates for worsening heart failure related hospitalizations in the two patient groups.

Adverse event definitions

Sustained ventricular and/or supraventricular arrhythmia (ventricular tachycardia, fibrillation, atrial fibrillation) events requiring further treatment or appropriate/inappropriate ventricular shock events, new-onset- IPE or hospitalization necessitating arrhythmias were collected as arryhtyhmic adverse events in both patient groups.

Multiple alert signs of potential device dysfunction (abrupty elevated pacing threshold, out of range pacing- or shock impedance value, low battery status, over/undersensing etc.) were monitored continuously and marked as device related adverse events.

Even nowadays the definition of worsening heart failure (WHF) event is not universally accepted [18] and this definition bias can lead consequentially to inproper event assesment, so we defined worsening heart failure event as at least one grade deterioration in New York Heart Association heart failure functional class (NYHA class) from baseline and further need of parenteral diuretic- and other medical therapy intensification because of heart failure symptoms.

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 regressional analysis were performed to confirm ststistically 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 or Table 1.

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) aswell 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 2. 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 Fig. 2.

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 2).

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 (15,529 ± 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 Fig. 3A, B. Post-hoc power analysis calculation for overall hospitalization outcome showed 98.9% and for worsening heart failure associated hospitalization 86% statistical power with 0.05 value of alpha.

Table 1 Baseline patient parameters

	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
Dyslipidaemia, 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**

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. The level of significance was defined as $p < 0.05$ (bold)

Arrhythmia events in the RMG were 2 cases of cumulated ventricular fibrillation/sustained ventricular tachycardia episodes and 2 cases of inappropriate ventricular shock due to high ventricular rate atrial fibrillation.

In the CFG 3 cases of cumulated sustained ventricular arrhythmia with or without adequate device therapy, 4 cases of atrial fibrillation with rapid venticular heart rate and 2 cases of inappropriate ventircular shocks were observed in the CFG. In one case of inappropriate ventircular shock atrial fibrillation with fast ventricular rate occured and in the other case shock-electrode impairment and noise oversensing was the underlying cause.

Correlational analysis

Spearman's rho correlational analysis and binary logistic regressional analysis showed statistical correlation for wosening heart failure events in patients with permanent atrial fibrillation ($p = 0.025$), higher baseline NYHA functional class ($p = 0.037$), decreased left ventricular ejection fraction ($p < 0.001$), increased left

Table 2 Event rates in patient groups at 6 and 12 months of follow up

	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

COVID-19 Corona virus disease 2019, *RMG* Remote monitoring group, *CFG* Conventionally followed group. The level of significance was defined as $p < 0.05$ (bold)

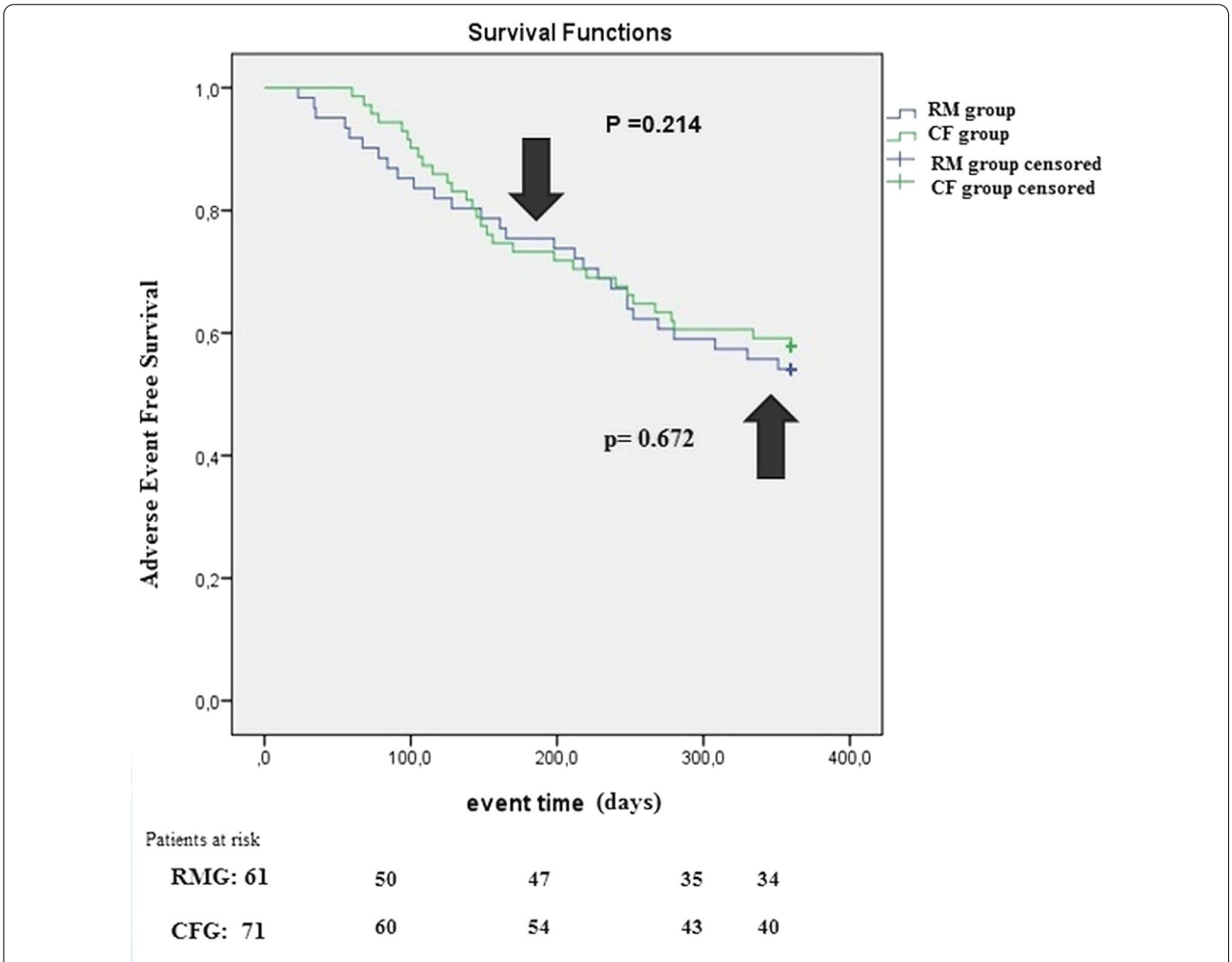

Fig. 2 Kaplan-Meiers curve: Adverse event-free survival. The composite end-point of device-, arrhythmia and worseing heart failure related adverse event-free survival is statistically non-differeing in the two observed patient groups neither at 180 days (log rank $p = 0.214$) nor at 360 days (log rank $p = 0.672$) of follow-up during the COVID-19 pandemic

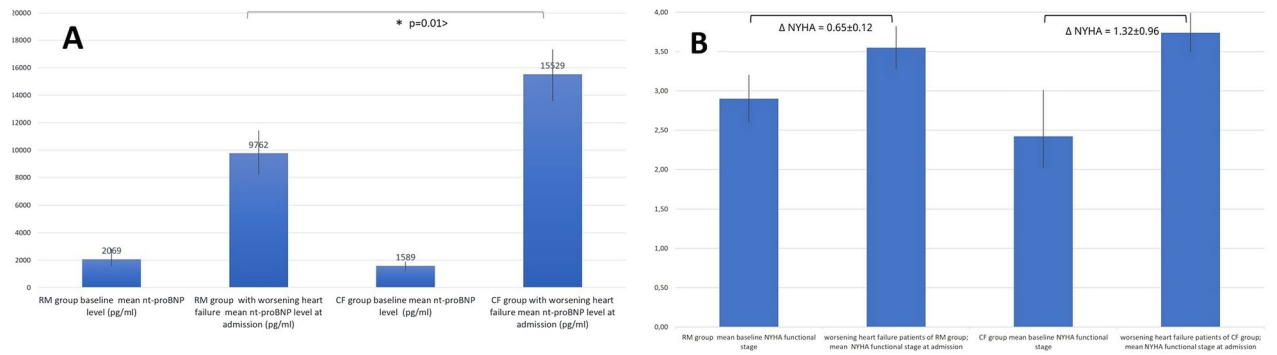

Fig. 3 Comparison of NT-proBNP levels (**A**) and change in NYHA functional class (**B**) at baseline and hospital admissions for worsening heart failure in the remote monitoring (RMG) and conventionally followed (CFG) patient groups. Patients in the conventionally followed group (CFG) had a significantly increased N terminal-proBNP (brain natriuretic peptide) levels at worsening heart failure event related hospital admissions (15,529 ± 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; $p = 0.026$)

ventricular end-diastolic ($p < 0.01$) and end-systolic ($p < 0.01$) diameters.

Patients with permanent atrial fibrillation ($p = 0.018$), increased left ventricular end-diastolic ($p < 0.01$) and end-systolic diamters ($p < 0.01$) and decreased left ventricular ejection fraction ($p < 0.01$) had independently higher risk for hospitalization for worsening heart failure.

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 surveilliance 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 [6, 7, 17]. 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. Recently D'Onofrio et al. introduced a validated multiparameter monitoring based prediction algorithm for heart failure hospitalizations in SELENE HF (Selection of potential predictors of worsening heart failure) trial [19]. A basline risk-stratifier Seattle HF Model was combined with temporal trend of various physiological (diurinal- and nocturnal heart rate, heart rate variability, physical activity) arrhythmia (ventricular extrasystoles, atrial fibrillation burden) and thoracic impedance parameters. Reaching the nominal index threshold of the algorithm, patients had substantially increased risk for heart failure hospitalization. The algorithm was showed to have an 65.5% sensitivity for an upcoming heart failure event with acceptable false/unexplained alert rate of 0.69 alert/patient/year.

The primary end-pont of our observational study was to asses the composite end-point of arrhythmia, device and worsening heart failure realted 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. [20] 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 comorbiditites, 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 tendeciously 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 tendenciously 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.

Abbreviations

ARNI: Angiotensin receptor blocker/nephrilisin inhibitor; COVID-19: Coronavirus disease 2019; CFG: Conventionally followed group; CRT-P/D: Cardiac resynchroinzation therapy pacemaker/defibrillator; CIED: Cardiac implantable electronic device; ICD: Implantable cardioverter defibrillator; IPE: In-office patient evaluation; NT pro-BNP: N terminal pro-brain natriuretic peptide; NYHA: New York heart association functional class; RMG: Remote monitoring group; RPM: Remote patient management; Sars Cov-2: Severe acute respiratory syndrome coronavirus type 2; WHF: Worsening of heart failure.

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Not applicable.

Author contributions

PE contributed in the conception of the work, conducting the study, data acquisition, revising the draft and agreed for all aspects of final version of the manuscript. MG contributed in the acquisition, analysis, or interpretation of data for the work and agreed for all aspects of the work. ISz contributed in revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AK contributed in the conception of the work, revising it critically for important intellectual content and contributed in final approval of the version to be published. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due patient privacy issues but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

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 the protocol was approved by the Ethics Committee of the University of Pécs (6600/2020).

Consent for publication

Written informed consent forms were obtained from all participants. The consent form also includes permission to publish. There is also an option to publish the patients' data with the approval of the ethics committee.

Competing interests

The authors declare that they have no competing interests.

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