Effect of remote monitoring on clinical outcomes in European heart failure patients with an implantable cardioverter-defibrillator: secondary results of the REMOTE-CIED randomized trial

Cheyenne S.L. Chiu [ID] [1]*, **Ivy Timmermans**[1,2], **Henneke Versteeg**[1], **Edgar Zitron**[3], **Philippe Mabo**[4], **Susanne S. Pedersen**[5,6], and **Mathias Meine**[1]; for the REMOTE-CIED Trial Investigators[†]

[1]Department of Cardiology, University Medical Centre Utrecht, Heidelberglaan 100, 3584 CX Utrecht, The Netherlands; [2]Department of Medical and Clinical, CoRPS—Center of Research on Psychology in Somatic Diseases, Tilburg University, Tilburg, The Netherlands; [3]Department of Cardiology, Universitätsklinikum Heidelberg, Heidelberg, Germany; [4]Department of Cardiology, Centre Hospitalier Universitaire, Rennes, France; [5]Department of Psychology, University of Southern Denmark, Odense, Denmark; and [6]Department of Cardiology, Odense University Hospital, Odense, Denmark

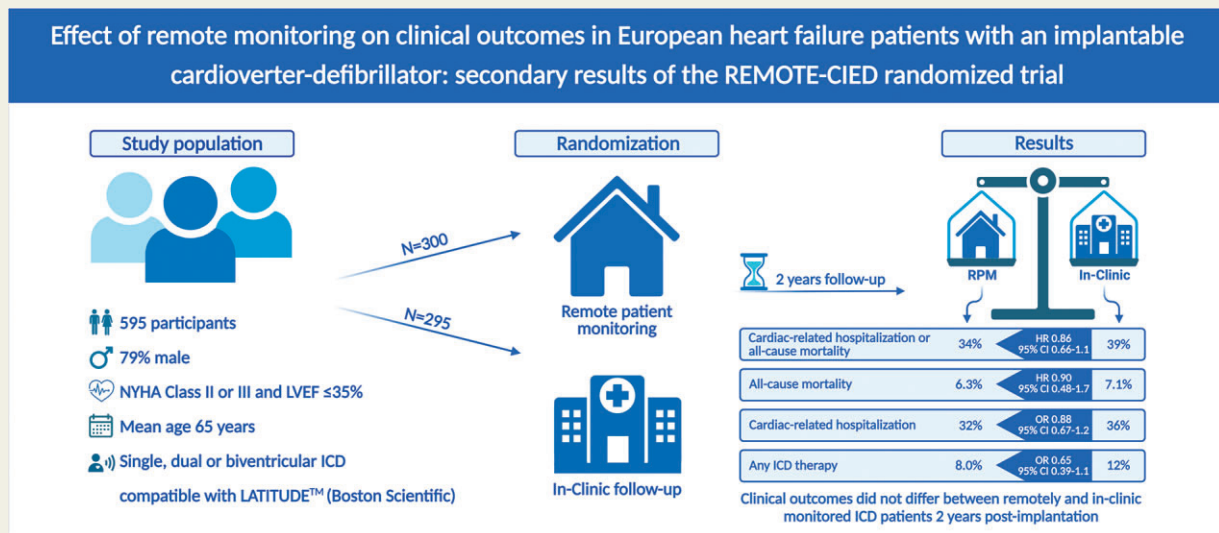|	
Aims	Remote patient monitoring (RPM) systems offer a promising alternative to conventional In-Clinic check-ups, hereby reducing unnecessary clinic visits. Especially with the rise of the COVID-19 pandemic, this reduction is of paramount importance. Regarding the association between RPM and clinical outcomes, findings of previous studies have been inconsistent. The aim of this study is to elucidate the effect of partly substituting In-Clinic visits by RPM on clinical outcomes in implantable cardioverter-defibrillator (ICD) patients.
Methods and results	The study included 595 heart failure patients (LVEF ≤35%; NYHA Class II/III) implanted with an ICD compatible with the Boston Scientific LATITUDE[TM] system. Participants were randomized to RPM plus an annual In-Clinic visit or 3–6 months In-Clinic check-ups alone. The investigated endpoints after 2 years of follow-up included a composite of all-cause mortality and cardiac hospitalization, mortality and cardiac hospitalization as independent endpoints and ICD therapy. The incidence of mortality and hospitalization did not differ significantly as independent, nor as composite endpoint between the RPM and In-Clinic group (all Ps <0.05). The results were similar regarding ICD therapy, except for appropriate ICD therapy (odds ratio 0.50; 95% confidence interval 0.26–0.98; $P = 0.04$). Exploratory subgroup analyses indicated that the effect of RPM differs between patients with specific characteristics, i.e. ≥60 years and permanent atrial fibrillation (all $Ps < 0.05$).
Conclusion	RPM is non-inferior to conventional In-Clinic visits regarding clinical outcomes. Routine In-Clinic follow-up may partly be substituted by RPM without jeopardizing safety and efficiency, and thus reducing unnecessary In-Clinic visits.
ClinicalTrials.gov identifier	NCT01691586.

---

*Corresponding author. E-mail address: m.meine@umcutrecht.nl

Graphical Abstract

Effect of remote monitoring on clinical outcomes in European heart failure patients with an implantable cardioverter-defibrillator: secondary results of the REMOTE-CIED randomized trial

What's new?

- The REMOTE-CIED study assessed the effect of remote patient monitoring on clinical outcomes by comparing RPM plus an annual In-Clinic visit vs. 3–6 months conventional In-Clinic visits alone.
- The results demonstrated that the incidence of mortality and hospitalization did not differ significantly as independent endpoints, nor as a composite event between remotely and In-Clinic-monitored patients in the first 2 years post-implantation.
- The incidence of ICD therapy subevents did not differ significantly between the RPM and In-Clinic group either, except for appropriate ICD therapy (4.3% RPM vs. 8.5% In-Clinic; $P = 0.04$).
- The clinical outcomes provide evidence that routine In-Clinic visits may partly be substituted by RPM without jeopardizing safety and efficiency, and thus reducing unnecessary clinic visits.

Introduction

Over the past decades, the number of patients suffering from heart failure has increased drastically and the indications for implantable cardioverter-defibrillators (ICDs) have expanded. In order to prevent death from life-threatening ventricular arrhythmias, heart failure patients are preferably treated with ICD therapy. The growing number of patients implanted with an ICD translates into an increasing demand for their follow-up.[1,2]

The introduction of remote patient monitoring (RPM) systems offer a promising alternative to conventional In-Clinic check-ups by sending disease- and ICD-related data to the hospital, hereby reducing unnecessary clinic visits.[3] The European Society of Cardiology (ESC) Guidelines on cardiac pacing and cardiac resynchronization therapy, developed in collaboration with the European Hearth Rhythm Association (EHRA) in 2013, recommend the use of RPM to provide earlier detection of clinical problems and technical issues.[4] Additionally, the ESC published a guidance document for the diagnosis and management of cardiovascular diseases during the COVID-19 pandemic in 2020. In this document, experts advocated substituting routine device interrogation clinic visits by RPM to the fullest extent as long as the pandemic status is maintained by the World Health Organization (WHO).[5] Furthermore, in a consensus statement in 2015, the Heart Rhythm Society (HRS) stated that remote monitoring should be offered to all patients implanted with a cardiac implantable electronic device (CIED) as part of the follow-up strategy.[6]

Large clinical trials and meta-analyses have already demonstrated that RPM is safe and effective in ICD patients. Regarding the association between RPM and clinical outcomes (e.g. mortality, hospitalization, and ICD therapy), findings of previous studies have been inconsistent. In the majority of the studies, RPM was used as an addition to conventional In-Clinic follow-up.[7–9] Those randomized controlled trials (RCTs) mostly reported neutral effects, whereas non-randomized clinical studies observed significantly reduced mortality and hospitalization rates.[10,11] The IN-TIME, TIM-HF2, and ECOST

randomized trials reinforced these clinical benefits. The IN-TIME and TIM-HF2 study concluded that RPM leads to a reduction in all-cause and cardiovascular mortality rates.[7,8] Lastly, the ECOST study showed that both the total number of given shocks and patients receiving inappropriate shocks was reduced in remotely monitored patients.[12] In more recent studies, RPM was partly substituted In-Clinic visits and the results were again conflicting. The RESULT study observed a reduced hospitalization rate and composite event of cardiovascular hospitalization and all-cause mortality in the RPM group.[13] In contrast, the MORE-CARE found no difference in the primary endpoint, defined as all-cause mortality and hospitalization for cardiovascular or device-related reasons.[14]

The European REMOTE-CIED study was primarily designed to be the first and largest RCT to investigate the effect of RPM on patient-reported ICD acceptance and disease-specific health status.[15] Usual care was partly replaced by RPM and the study was performed under daily practice reflecting circumstances. This distinguishes the REMOTE-CIED trial from previously conducted trials, as those trials intensified follow-up by using RPM as an addition to conventional In-Clinic follow-up, daily data transmission, or integrating a central monitoring unit.[7–9] The results of the REMOTE-CIED study showed no difference in heart failure-specific health status or ICD acceptance between the remotely and In-Clinic monitored patients in the first 2 years after implantation.[16–18] The influence of replacing In-Clinic follow-up by RPM on mortality, hospitalization, and ICD therapy in heart failure patients with an implanted ICD/CRT-D was investigated as secondary outcomes during the REMOTE-CIED trial. The aim of this article is to elucidate the effect of substituting In-Clinic follow-up by RPM on these clinical outcomes.

Methods

Study design and participants

A detailed description of the study design has been published previously.[15] In brief, the European REMOTE-CIED study was a prospective, multicentre, randomized trial, monitoring 595 heart failure patients implanted with an ICD/cardiac resynchronization therapy defibrillator (CRT-D) for 2 years post-implantation. The participating centres consisted of 32 general and academic hospitals in France, Germany, The Netherlands, Spain, and Switzerland. Selection criterion for participating was an existing infrastructure for RPM and experience with the LATITUDE™ system.

Between April 2013 and January 2016, patients were recruited and screened for eligibility by local investigators. Patients were eligible for participation if they (i) received a *de novo* ICD (single chamber/dual chamber/biventricular) compatible with the LATITUDE™ Patient Management System (Boston Scientific) in one of the participating centres and (ii) suffered from symptomatic heart failure [Left ventricular ejection fraction (LVEF) ≤35% and New York Heart Association (NYHA) functional Class II or III]. Exclusion criteria were not met if the patient was (i) younger than 18 or older than 85 years of age, (ii) on the waiting list for a heart transplantation, (iii) had a history of psychiatric illness other than affective/anxiety disorders, (iv) was unable to complete the questionnaire due to cognitive impairments, or (v) had insufficient knowledge of the language in the country where patients were recruited.

All participants received written and oral information about the study and provided written informed consent. The trial was conducted in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was approved by the medical ethics committees of all participating centres and the trial is registered on ClinicalTrials.gov under study ID NCT01691586.

After recruitment, patients were randomized in a 1:1 fashion to either RPM plus annual In-Clinic follow-up (RPM group) or In-Clinic follow-up only (In-Clinic group) with the use of a blocked randomized procedure. To ensure that the relative percentage of ICD and cardiac resynchronization therapy defibrillator (CRT-D) patients was equal in both the RPM and In-Clinic groups, a separate randomization procedure was used within these two subsets of patients.

In compliance with the ACC/AHA/HRS guidelines, patients randomized to the RPM group had scheduled In-Clinic visits at 12 and 24 months post-implantation.[19] The intermediate ICD check-ups were performed remotely at least every 6 months and data similar to that of an In-Clinic device interrogation were gathered. Patients randomized to the In-Clinic group visited the outpatient clinic (at least) every 3–6 months, according to the participating centres' standard clinical routine. The ICD programming in all patients as well as the programming of the remote monitoring alerts were at the discretion of the implanting centre.

Baseline characteristics

At baseline, information on patients' clinical characteristics was extracted from their medical records and documented in an electronic case report form by local investigators. This information included ICD/heart failure characteristics, medication, and comorbidities. In both groups, patients received baseline and follow-up questionnaires regarding socio-demographics, lifestyle behaviour, psychological characteristics, ICD acceptance, and heart failure-related health status. These questionnaires and results of the primary outcomes have been discussed in greater detail in previous published articles.[16–18]

Clinical outcomes

In order to assess the influence of RPM on clinical outcomes, information on cardiac-related hospitalization, mortality (all-cause and cardiac), and time to first ICD therapy was extracted from patients' medical records and gathered via electronic case report forms at baseline (T_0), 3 (T_1), 6 (T_2), 12 (T_3), and 24 months (T_4) post-implantation. The time to first ICD therapy was subdivided as follows: (i) any ICD therapy (shock/ATP/appropriate/inappropriate), (ii) appropriate ICD therapy (shock/ATP), (iii) inappropriate ICD therapy (shock/ATP), (iv) appropriate ICD shock, and (v) inappropriate ICD shock.

Sample size calculation and statistical analysis

The sample size calculation has been presented in detail elsewhere.[15,16] Patient characteristics are reported as frequencies with percentages [*N* (%)] for categorical variables, and medians with inter-quartile ranges [median (IQR)] for continuous variables, as the data followed a non-Gaussian distribution. In order to detect statistically significant differences between the study arms, the Pearson's χ^2 test (or Fisher's exact test if appropriate), and Mann–Whitney *U* test were applied to categorical variables and continuous variables, respectively. All events regarding hospital admission, mortality, and ICD therapy from the day of signing informed consent to 24 months post-implantation or premature study termination were included in the analyses. The Cox proportional hazards model was used to perform *post hoc* survival analyses on these clinical outcomes.

In addition to the intention-to-treat analyses, per-protocol analyses excluding all crossovers were performed, taking the relative high number of patients who switched study arms into account (15 RPM and 34 In-

Table 1 **Baseline characteristics of the total sample, and stratified by randomization group[a]**

	Total sample (n = 595)	RPM group (n = 300)	In-Clinic group (n = 295)
Age (years)	65 (59–73)	66 (58–73)	65 (59–73)
Female	123 (21)	67 (22)	56 (19)
Device/health failure characteristics			
Type of ICD			
Single chamber	256 (43)	126 (42)	130 (44)
Dual chamber	109 (18)	60 (20)	49 (17)
Biventricular	230 (39)	114 (38)	116 (39)
Secondary prophylactic ICD indication	86 (15)	42 (14)	44 (15)
Ischaemic heart failure aetiology	336 (57)	158 (53)	128 (60)
QRS duration (ms)	120 (102–156)	118 (102–157)	124 (102–154)
Ejection fraction (≤3 months pre-implantation)	27 (22–31)	27 (21–31)	28 (22–31)
New York Heart Association Class III	197 (33)	98 (33)	99 (34)
Cardiac medication			
ACE inhibitors + ARBs	525 (88)	267 (89)	258 (88)
Beta-blockers (excluding sotalol)	497 (84)	247 (82)	250 (85)
Diuretics	431 (72)	217 (72)	214 (73)
Aldosterone antagonists	370 (62)	177 (59)	193 (65)
Antiarrhythmic medication (including sotalol)	98 (17)	49 (16)	49 (17)
Comorbidities			
Diabetes mellitus	192 (32)	90 (30)	102 (35)
Chronic obstructive pulmonary disease	84 (14)	45 (15)	39 (13)
Renal disease (GFR <60 mL/min/1.73 m^2)	148 (25)	75 (25)	73 (25)
Atrial fibrillation	168 (28)	85 (28)	83 (28)
Hypertension	347 (58)	171 (57)	176 (60)
Anaemia (HB <8.6/<7.4 mmol/L—males/females)	63 (11)	29 (10)	34 (12)

Results are presented as frequencies with percentages [N (%)] for categorical variables, and medians with inter-quartile ranges [median (IQR)] for continuous variables. All comparisons between the two groups were insignificant (all Ps > 0.05).

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; GFR, glomerular filtration rate; HB, haemoglobin; ICD, implantable cardioverter-defibrillator; RPM, remote patient monitoring.

[a]Intention-to-treat.

Clinic). All performed tests were two-tailed, and P values ≤0.05 indicated statistical significance. Analyses were performed with SPSS 22.0 (SPSS Inc., Chicago, IL, USA), and SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Sample characteristics

The process of patients' enrolment, allocation, and follow-up has been described in detail elsewhere.[16] After enrolment and allocation, the final study sample for the intention-to-treat analysis consisted of 595 patients. The RPM group yielded a total of 300 patients and 295 patients were allocated to the In-Clinic arm.

Baseline characteristics of the total study sample, including device/heart failure characteristics, cardiac medication, and comorbidities, are stratified by randomization group and present in Table 1.

Mortality and cardiac hospitalization

The number of all-cause mortality and cardiac hospitalization were combined and analysed as a composite event. The proportion of affected patients did not differ significantly between the RPM and In-

Clinic group (101 vs. 114, P = 0.21). Furthermore, the Cox regression model showed no significant between-group difference in time to first cardiac hospitalization or all-cause mortality [hazard ratio (HR) 0.86; 95% confidence interval (CI) 0.66–1.1; P = 0.27]. The calculated frequency, HR/odds ratio (OR), 95% CI, and P values for all-cause mortality or cardiac hospitalization and other events are listed in Table 2. The mortality and hospitalization rates were further evaluated as independent endpoints. At the end of the study, 19 (6.3%) of 300 patients in the RPM group and 21 (7.1%) of 295 in the In-Clinic group had deceased. Of those deaths, 10 (3.3%) vs. 8 (2.7%) were caused by cardiac disease. The number of all-cause and cardiac deaths did not differ significantly between the study arms (P = 0.70 all-cause, P = 0.66 cardiac). The survival analysis demonstrated no statistically significant differences for neither time to all-cause mortality (HR 0.90; 95%; CI 0.48–1.7; P = 0.73), nor cardiac mortality (HR 1.2; 95%; CI 0.49–3.1; P = 0.65). With respect to the hospitalization rate, the number of cardiac hospital admissions did not differ significantly between the remotely and In-Clinic monitored patients (96 vs. 106, P = 0.31) and no association between the time to first cardiac hospitalization and study group was indicated (HR 0.88; 95% CI 0.67–1.2; P = 0.36). However, the number of visits per patient per year was significantly

Table 2 Effect of RPM on clinical event rates over 24 months' follow-up[a]

Event	RPM group (n = 300)	In-Clinic group (n = 295)	HR/OR	95% CI	P value
Cardiac-related hospitalization or all-cause mortality	101 (34)	114 (39)	0.86	0.66–1.1	0.27
Cardiac-related hospitalization	96 (32)	106 (36)	0.88	0.67–1.2	0.36
All-cause mortality	19 (6.3)	21 (7.1)	0.90	0.48–1.7	0.73
Cardiac mortality	10 (3.3)	8 (2.7)	1.2	0.49–3.1	0.65
Any ICD therapy	24 (8.0)	36 (12)	0.65	0.39–1.1	0.09
Appropriate ICD therapy	13 (4.3)	25 (8.5)	0.50	0.26–0.98	**0.04**
Inappropriate ICD therapy	8 (2.7)	7 (2.4)	1.1	0.41–3.1	0.82
Any ICD shock	21 (7.0)	32 (11)	1.0	0.60–1.8	0.87
Appropriate ICD shock	14 (4.7)	21 (7.1)	0.53	0.24–1.2	0.11
Inappropriate ICD shock	10 (3.3)	7 (2.4)	1.29	0.43–3.8	0.65

Results are presented as number of patients with percentages [N (%)]. Significant results (P < 0.05) are printed in bold. The HR/OR and 95% CI are shown with the In-Clinic group as reference.
CI, confidence interval; HR, hazard ratio; OR, odds ratio; RPM, remote patient monitoring.
[a]Intention-to-treat.

lower in remotely monitored patients (1.46 RPM vs. 2.23 UC; P < 0.001).

Impact of remote patient monitoring on implantable cardioverter-defibrillator therapy

The impact of RPM on ICD therapy was evaluated and subdivided in the following events: any ICD therapy, appropriate ICD therapy, inappropriate ICD therapy, any shock, appropriate shock, and inappropriate shock. *Post hoc* Pearson's χ^2 tests and survival analyses detected no significant difference between the randomization groups in any subdivided event, with the exception of appropriate ICD therapy. At the time of study completion, 13 remotely vs. 25 In-Clinic monitored patients had undergone appropriate ICD therapy (P = 0.04). Finally, a significant difference was indicated between the randomization groups and time to first appropriate ICD therapy (HR 0.5; 95% CI 0.26–0.98; P = 0.04). The calculated details of all subdivided events are present in Table 2.

Exploratory analysis of subgroups

In an exploratory analysis, clinical outcomes were assessed within subgroups. The results are present in *Figure 1* (All-cause mortality and cardiac hospitalization composite), *Figure 2* (Any ICD therapy), *Figure 3* (Appropriate ICD therapy), and *Figure 4* (Inappropriate ICD therapy). No significant interactions were perceived between specific patient characteristics and RPM utilization for the composite event or inappropriate ICD therapy, but were indicated for any and appropriate ICD therapy. Regarding any ICD therapy event, the probability of undergoing therapy was lower in remotely monitored patients ≥60 years of age (OR 0.50; 95% CI 0.27–0.91; P = 0.02). Furthermore, patients >60 years of age or suffering from permanent atrial fibrillation in the RPM group were less likely to receive appropriate ICD therapy compared with the In-Clinic group (OR 0.37; 95% CI 0.17–0.85; P = 0.013 and OR 0.075; 95% CI 0.009–0,61; P = 0.002, respectively).

Discussion

According to our findings, the partial substitution of conventional In-Clinic follow-up by RPM in patients implanted with an ICD did not lead to significant differences in mortality (all-cause or cardiac) or cardiac hospitalization as independent endpoints, nor as a composite event in the first 2 years post-implantation. Regarding the impact of remote monitoring on ICD therapy, no significant differences were demonstrated between the randomization groups in any previously defined subevents, except for appropriate therapy (OR 0.50; 95% CI 0.26–0.98; P = 0.04). The probability of remotely monitored patients undergoing appropriate ICD therapy was reduced by half in comparison with the In-Clinic group. An additional per-protocol analysis was performed and demonstrated results consistent with the intention-to-treat analysis. However, the observed lowering effect of RPM on the odds of undergoing appropriate ICD therapy was diminished to an insignificant size (P = 0.25). Nonetheless, the trend of a lower appropriate therapy probability in remotely monitored patients persisted (HR 0.66; 95% CI 0.32–1.3). Recent developments of algorithms for the early detection of progression of heart failure such as HeartLogic[TM] may improve remote heart failure monitoring and reduce hospitalization.

The subgroup analysis of REMOTE-CIED patients indicated that the effect of patient management guided by RPM differs between patients with specific characteristics. Remotely monitored patients ≥60 years of age or suffering from permanent atrial fibrillation had a smaller chance of receiving appropriate ICD therapy in comparison with the In-Clinic group. Furthermore, a lower probability of receiving any ICD therapy was observed in patients ≥60 years in the RPM group compared with the In-Clinic group. A subanalysis of the IN-TIME study concluded that the absolute benefit from RPM seems to be higher in high-risk patients with worse prognosis, but this was only broadly assessed by comparing ICD with CRT-D patients.[20] In order to provide personalized care, further research is warranted to investigate the effect of RPM on specific subgroups of patients.
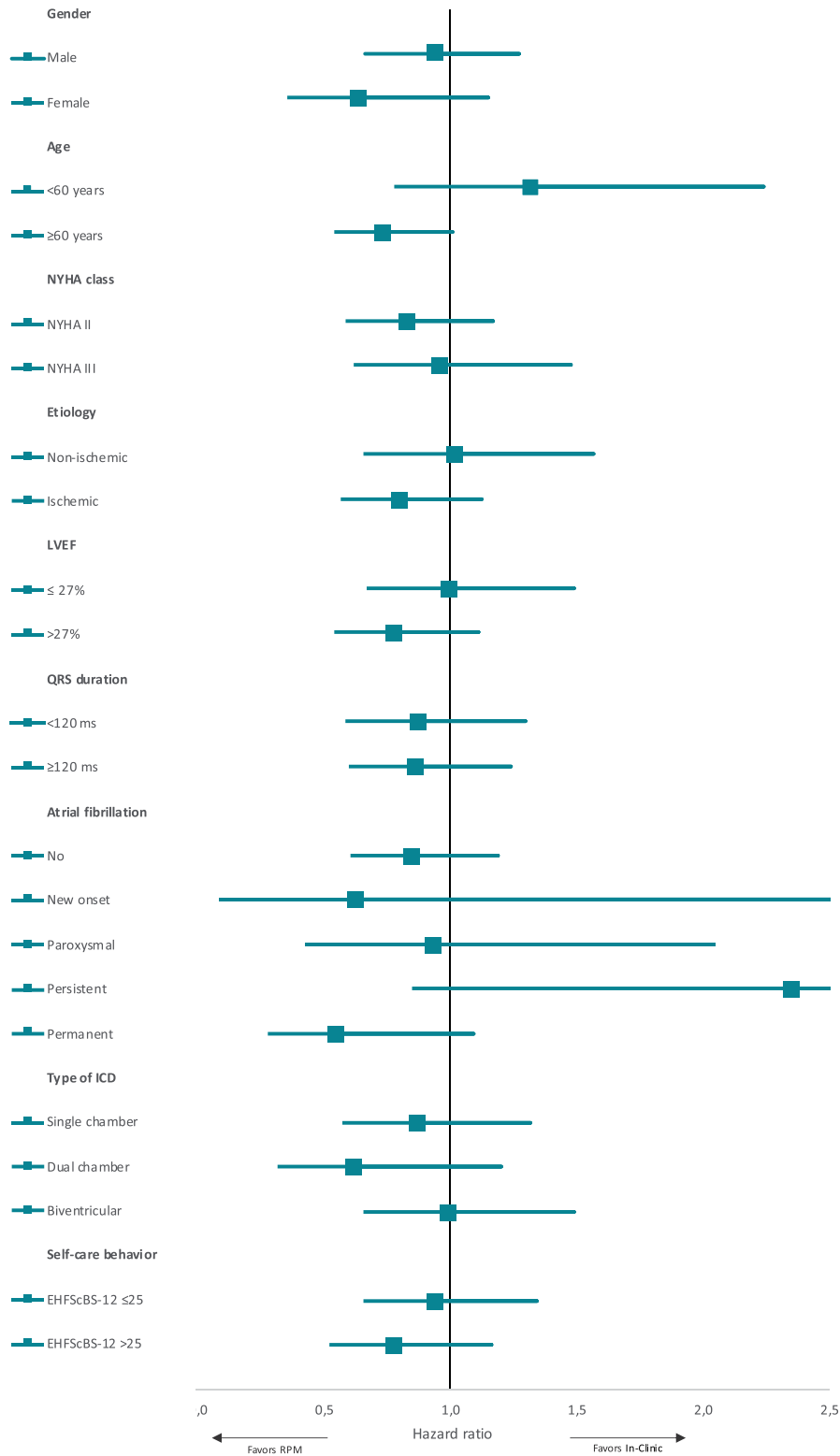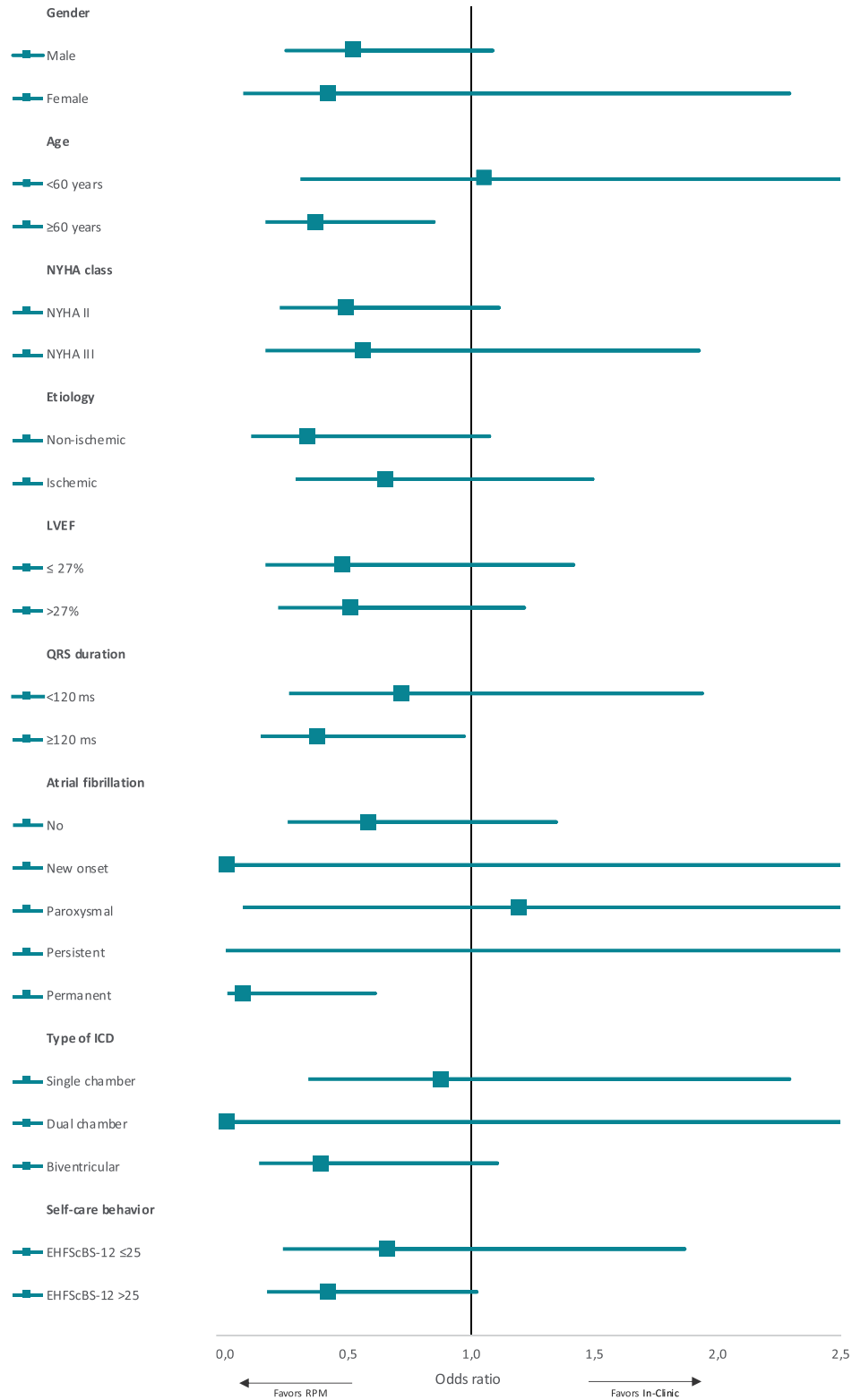
Figure 1 Forest plot of subgroup analysis for the risk of all-cause mortality or cardiac hospitalization composite.[a] Clinical characteristics as measured at baseline. The hazard ratio and 95% confidence interval are shown with the In-Clinic group as reference. [a]Intention-to-treat. EHFScBS-12, European Heart Failure Self Care Behaviour Scale (range 12–60, higher score indicates worse self-care behaviour); ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
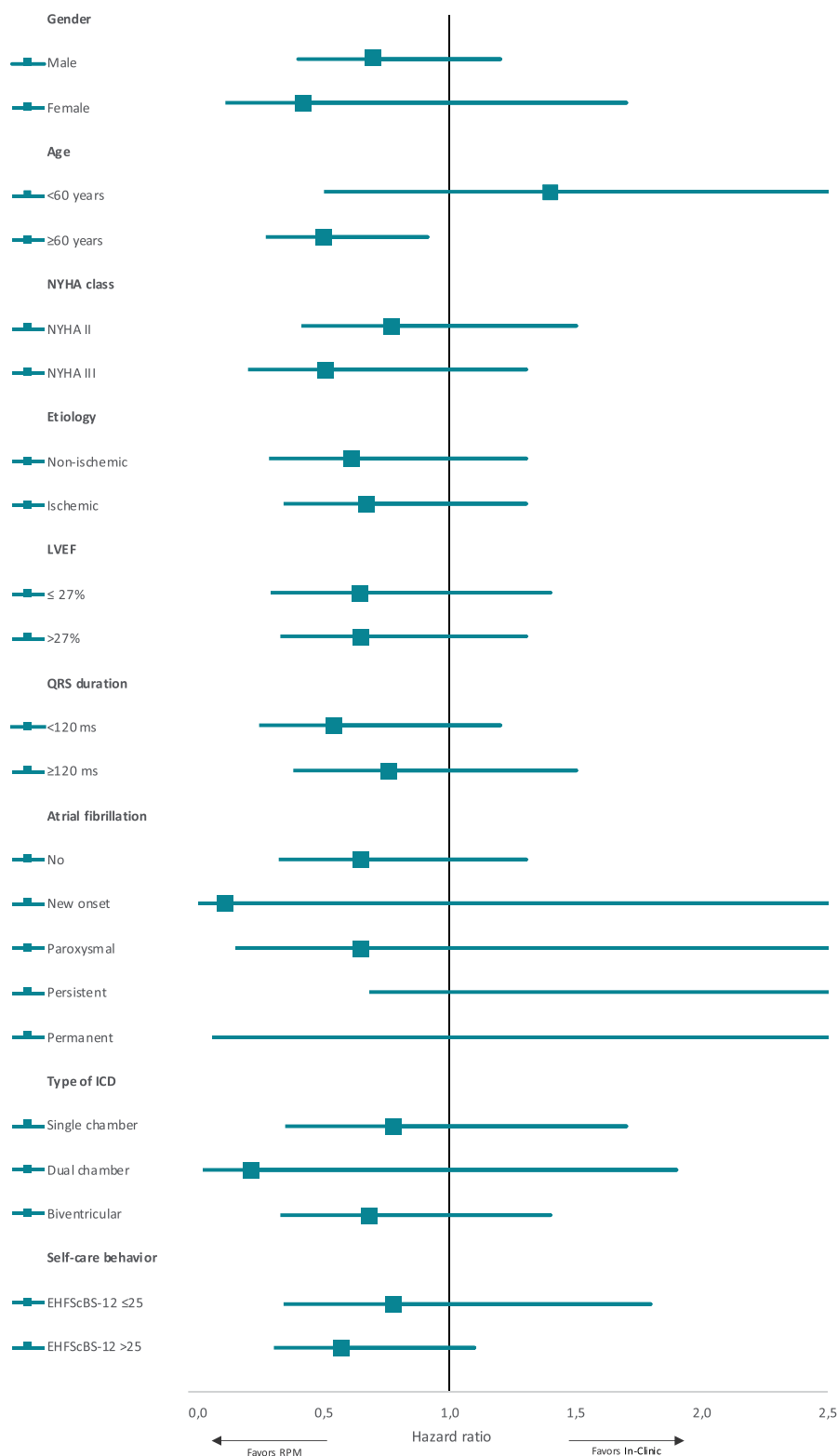
Figure 2 Forest plot of subgroup analysis for the probability of undergoing any ICD therapy.[a] Clinical characteristics as measured at baseline. The odds ratio and 95% confidence interval are shown with the In-Clinic group as reference. [a]Intention-to-treat. EHFScBS-12, European Heart Failure Self Care Behaviour Scale (range 12–60, higher score indicates worse self-care behaviour); ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Figure 3 Forest plot of subgroup analysis for the probability of undergoing appropriate ICD therapy.[a] Clinical characteristics as measured at baseline. The odds ratio and 95% confidence interval are shown with the In-Clinic group as reference. [a]Intention-to-treat.EHFScBS-12, European Heart Failure Self Care Behaviour Scale (range 12–60, higher score indicates worse self-care behaviour); ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

In essence, the results of the current study provide evidence that RPM is non-inferior to In-Clinic follow-up with respect to clinical outcomes. Several previously conducted studies did observe improved clinical outcomes in remotely monitored patients.[7–9,13] However, the applied study designs differed from the REMOTE-CIED trial. Meta-analyses have indicated that intensifying follow-up with daily transmission and verification of data and predefined response mechanisms to RPM-alerts, improve clinical outcomes.[10,21] The only RCT to date (IN-TIME) that detected a significantly decreased mortality risk, adopted this intensified follow-up by using a central monitoring unit. Moreover, RPM was used on top of usual care.[7] Details of all studies discussed in this section are present in *Table 3*. After 12 months of follow-up, the all-cause mortality rate was 3.4% in the RPM vs. 8.7% in the control group (HR 0.36; 95% CI 0.17–0.74; $P = 0.004$). This number of all-cause deaths in the control group is remarkably high in comparison with the In-Clinic group (3.5%) in the REMOTE-CIED study after 12 months and could consequently have increased statistical significance. In addition, in the IN-TIME study a total of 99 additional in clinic follow-up visits were required for 63 (19%) remotely monitored patients, corresponding to 0.32 extra visits per patient–year. The total number of visits was also increased in the RPM group (985 RPM vs. 844 UC). In contrast, in the REMOTE-CIED study, a beneficial trend in favour of the RPM group was observed relating to unscheduled visits (47 RPM patients vs. 66 UC; $P = 0.057$). The reduced mortality risk in the IN-TIME RPM group could partly be attributed to potential undertaken interventions during unscheduled visits.[11]

Another RCT (TIM-HF2) demonstrated that offering support from a telemedical centre 24/7, conducting monthly telephone interviews and transmitting data daily resulted in a significantly reduced mortality rate in heart failure patients (7.9% RPM vs. 11% UC; $P = 0.028$).[8] Again, these mortality rates are high in comparison with the REMOTE-CIED study (1-year mortality: 3.1% RPM vs. 3.5% UC), and could subsequently have increased statistical significance.

In contrast to the studies mentioned above, In-Clinic visits were partly substituted in the RESULT and MORE-CARE studies.[13,14] In the RESULT study, the primary endpoint (all-cause mortality and cardiovascular hospitalization) occurred significantly less frequently in the RPM group in comparison with the UC group (39.5% RPM and 48.5% UC; $P = 0.048$) and the same conclusion was drawn regarding the cardiovascular hospitalization rate (37.1% RPM vs. 45.5% UC; $P = 0.045$). Remotely monitored patients only had a scheduled clinic visit at 12 months post-implantation. However, data were analysed daily by the central remote monitoring office. The MORE-CARE study showed a significant 38% reduction in health-care utilization, defined as cardiovascular hospitalizations, emergency department visits and in-office follow-ups, in the RPM group (IRR 0.62; 95% CI 0.58–0.66; $P < 0.001$), whereas results regarding mortality and hospitalization remained neutral.

Integrating an intensified follow-up routine with RPM in addition to conventional care, a central monitoring unit or a telemedical centre, would lead to an even higher workload instead of health care burden relief. This is particularly undesirable during the current COVID-19 pandemic. In addition, the REM-HF study reported that only 3534 (<8%) out of 79 325 reviewed data transmissions required an intervention during 2 years of follow-up.[9] Medication had to be changed after merely 226 (<0.5%) transmissions. However, this excessive number of transmissions did not result in reduced mortality or hospitalization rates. RPM was used on top of usual care in this study.

In relation to ICD therapy, the ECOST study is the only RCT that has detected significantly reduced shock risks.[12] Both the total number of shocks and patients receiving inappropriate shocks were diminished (193 RPM vs. 657 UC; $P < 0.05$ and 11 RPM vs. 22 UC; $P < 0.05$, respectively), whereas no difference in mortality or hospitalization was observed in 2 years of follow-up. Besides, the number of visits per patient per year was significantly lower in remotely monitored patients (1.46 RPM vs. 2.23 UC; $P < 0.001$).

Earlier, the REMOTE-CIED study already provided evidence that partly substituting In-Clinic visits by RPM does not influence patient-reported health status, nor ICD acceptance or treatment satisfaction.[16,17] The present paper has proven that even without implementing a central monitoring unit, 24/7 available telemedical support, and daily or weekly data transmission, RPM is non-inferior to usual care regarding clinical outcomes. Thus, remote monitoring systems do not have to be used on top of usual care to reduce the number of unnecessary clinic visits without jeopardizing safety and efficiency. Therefore, we would recommend making the use of RPM systems standard practice.

Limitations

As the majority of studies, the current study was subject to potential limitations. The first limitation concerns the relative high number of dropouts and crossovers, which has impacted the statistical power of our analysis negatively. An additional per-protocol analysis excluding all crossovers was performed in order to correct for this. Secondly, the study sample consisted of relatively young patients (mean age 65) with mild heart failure (67% NYHA II) and the results may therefore not be generalizable to older patients with severe heart failure. Furthermore, an RPM system from a single manufacturer was used in this study: the LATITUDE[TM] Patient Management system from Boston Scientific. Differences in the various available systems exist and could subsequently lead to inconsistent outcomes.[10] Another limitation concerns the remarkably low incidence of inappropriate ICD therapy in the REMOTE-CIED study (2.7% RPM vs. 2.4% In-Clinic). Our study started in 2013, and several studies about ICD programming to avoid unnecessary ICD therapy had already been published.[22–24] Finally, it is important to consider that the *post hoc* subanalysis was of an explorative nature and might lack sufficient power, as the number of events in specific subgroups was low. Nevertheless, these results could provide indications for further research.

Conclusion

The clinical endpoints of the REMOTE-CIED study demonstrated that the partial substitution of In-Clinic follow-up by RPM in patients with heart failure did not have an effect on the rate of all-cause mortality and cardiac hospitalization combined, (all-cause mortality or cardiac) mortality, cardiac hospitalization or ICD therapy. The conclusion can be drawn that partly substituting routine In-Clinic visits for device interrogation by RPM is safe and effective.

Table 3 Detailed characteristics and eligibility criteria of discussed previously conducted studies

Study	RPM group FU	Control group FU	Sample size (n)	FU duration (months)	LVEF (%)	NYHA class	CIED type
IN-TIME[7]	Clinic visits according to clinical standard at participating centre; RPM on top of UC	Clinic visits according to clinical standard at participating centre	716	12	≤35	NYHA II–III	Biotronik Lumax ICD/CRT-D
TIM-HF 2[8]	Clinic visits according to clinical standard at participating centre; RPM on top of UC	Clinic visits according to clinical standard at participating centre	1571	13	≤45 (or >45 + diuretics)	NYHA II–III	No CIED, ICD or CRT-D
RESULT[13]	Clinic visit at 12 months; RPM replaced In-Clinic visit at 3, 6, and 9 months	Clinic visit every 3 months	600	12	≤35	NYHA II–IV	St Jude, Biotronik, Medtronic, Boston ICD/CRT-D
MORE-CARE[14]	Clinic visit every 8 months; RPM replaced In-Clinic visits at 8, 16, and 24 months	Clinic visit every 4 months	865	24	≤35	NYHA III–IV	Medtronic CRT-D with OptiVol
REM-HF[9]	Clinic visit every 3/6 months; RPM on top of UC	Clinic visit every 3/6 months	1650	Median 33.6	No criterium specified	NYHA II–IV	Medtronic, Boston Scientific, St. Jude Medical ICD/CRT-D/CRT-P
ECOST[12]	Clinic visit at 12 and 24 months; RPM replaced In-Clinic visits at 6 and 18 months.	Clinic visit every 6 months	433	24	No criterium specified	NYHA I–III	Biotronik ICD

CIED, cardiac implantable electronic device; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ECOST, Costs of remote monitoring vs. ambulatory follow-ups of implanted cardioverter-defibrillators; FU, follow-up; ICD, implantable cardioverter device; IN-TIME, Influence of home monitoring on mortality and morbidity in heart failure patients with impaired left ventricular; LVEF, left ventricular ejection fraction; MORE-CARE, Monitoring resynchronization devices and cardiac patient; NYHA, New York Heart Association; REM-HF, Remote management of heart failure using implantable electronic devices; RPM, remote patient monitoring; RESULT, Remote supervision to decrease hospitalization rate; TIM-HF2, Telemedical interventional management in patients with heart failure; UC, usual care.
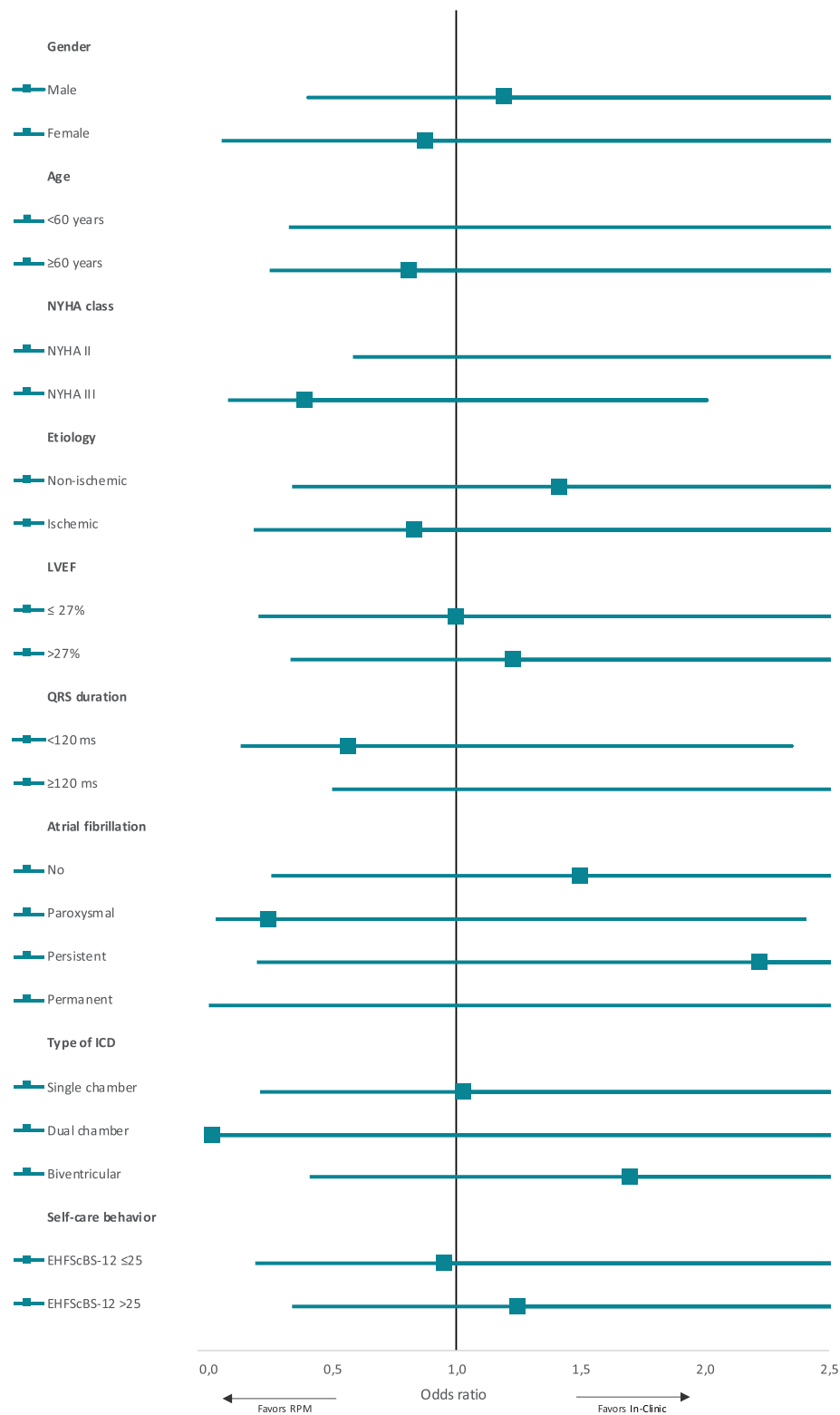
Figure 4 Forest plot of subgroup analysis for the probability of undergoing inappropriate ICD therapy.[a] Clinical characteristics as measured at baseline. The odds ratio and 95% confidence interval are shown with the In-Clinic group as reference. No patients with new onset atrial fibrillation had undergone inappropriate ICD therapy. Hence, new onset atrial fibrillation could not be plotted. [a]Intention-to-treat. EHFScBS-12, European Heart Failure Self Care Behaviour Scale (range 12–60, higher score indicates worse self-care behaviour); ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Supplementary material

Data availability

The data underlying this article cannot be shared publicly for the privacy of individuals that participated in the study. The data will be shared on reasonable request to the corresponding author.

References

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N *et al.* Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**: 1789–858.

2. Wijers SC, van der Kolk BYM, Tuinenburg AE, Doevendans PAF, Vos MA, Meine M *et al.* Implementation of guidelines for implantable cardioverter-defibrillator therapy in clinical practice: which patients do benefit? *Neth Heart J* 2013;**21**: 274–83.

3. Dubner S, Auricchio A, Steinberg JS, Vardas P, Stone P, Brugada J *et al.* ISHNE/EHRA expert consensus on remote monitoring of cardiovascular implantable electronic devices (CIEDs). *Europace* 2012;**14**:278–93.

4. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt O-A. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace* 2013;**15**:1070–118.

5. Andreini D, Arbelo E, Barbato E, Bartorelli AL, *et al.* 'ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic'. *Escardio.org*, 2020. https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance#p09 (2 February 2021, date last accessed).

6. Slotwiner D, Varma N, Akar JG, Annas G, Beardsall M, Fogel RI *et al.* HRS expert consensus statement on remote interrogation and monitoring for cardiovascular implantable electronic devices. *Heart Rhythm* 2015;**12**:e69–100.

7. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A *et al.* Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *Lancet* 2014;**384**:583–90.

8. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan B-A *et al.* Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. *The Lancet* 2018;**392**:1047–57.

9. Morgan JM, Kitt S, Gill J, McComb JM, Ng GA, Raftery J *et al.* Remote management of heart failure using implantable electronic devices. *Eur Heart J* 2017;**38**: 2352–60.

10. Parthiban N, Esterman A, Mahajan R, Twomey DJ, Pathak RK, Lau DH *et al.* Remote Monitoring of implantable cardioverter-defibrillators: a systematic review and meta-analysis of clinical outcomes. *J Am Coll Cardiol* 2015;**65**:2591–600.

11. Klersy C, Boriani G, De Silvestri A, Mairesse GH, Braunschweig F, Scotti V *et al.*; for the Health Economics Committee of the European Heart Rhythm Association. Effect of telemonitoring of cardiac implantable electronic devices on healthcare utilization: a meta-analysis of randomized controlled trials in patients with heart failure. *Eur J Heart Fail* 2016;**18**:195–204.

12. Guedon-Moreau L, Lacroix D, Sadoul N, Clementy J, Kouakam C, Hermida J-S *et al.*; for the ECOST trial Investigators. A randomized study of remote follow-up of implantable cardioverter defibrillators: safety and efficacy report of the ECOST trial. *Eur Heart J* 2013;**34**:605–14.

13. Tajstra M, Sokal A, Gadula-Gacek E, Kurek A, Wozniak A, Niedziela J *et al.* Remote supervision to decrease hospitalization rate (RESULT) study in patients with implanted cardioverter-defibrillator. *Europace* 2020;**22**:769–76.

14. Boriani G, Da Costa A, Quesada A, Ricci RP, Favale S, Boscolo G *et al.*; on behalf of the MORE-CARE Study Investigators. Effects of remote monitoring on clinical outcomes and use of healthcare resources in heart failure patients with biventricular defibrillators: results of the MORE-CARE multicentre randomized controlled trial. *Eur J Heart Fail* 2017;**19**:416–25.

15. Versteeg H, Pedersen SS, Mastenbroek MH, Redekop WK, Schwab JO, Mabo P *et al.* Patient perspective on remote monitoring of cardiovascular implantable electronic devices: rationale and design of the REMOTE-CIED study. *Neth Heart J* 2014;**22**:423–8.

16. Versteeg H, Timmermans I, Widdershoven J, Kimman G-J, Prevot S, Rauwolf T *et al.* Effect of remote monitoring on patient-reported outcomes in European heart failure patients with an implantable cardioverter-defibrillator: primary results of the REMOTE-CIED randomized trial. *Europace* 2019;**21**:1360–8.

17. Timmermans I, Meine M, Szendey I, Aring J, Romero Roldán J, van Erven L *et al.* Remote monitoring of implantable cardioverter defibrillators: patient experiences and preferences for follow-up. *Pacing Clin Electrophysiol* 2019;**42**:120–9.

18. Timmermans I, Versteeg H, Meine M, Pedersen SS, Denollet J. Illness perceptions in patients with heart failure and an implantable cardioverter defibrillator dimensional structure, validity, and correlates of the brief illness perception questionnaire in Dutch, French and German patients. *J Psychosom Res* 2017;**97**:1–8.

19. Wilkoff BL, Auricchio A, Brugada J, Cowie M, Ellenbogen KA, Gillis AM *et al.*; Heart Failure Society of America. HRS/EHRA expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs). *Heart Rhythm* 2008; **5**:907–25.

20. Geller JC, Lewalter T, Bruun NE, Taborsky M *et al.* Implant-based multiparameter telemonitoring of patients with heart failure and a defibrillator with vs. without cardiac resynchronization therapy option: a subanalysis of the IN-TIME trial. *Clin Res Cardiol* 2019;**108**:1117–27.

21. Hindricks G, Varma N, Kacet S, Lewalter T, Søgaard P, Guédon-Moreau L *et al.* Daily remote monitoring of implantable cardioverter-defibrillators: insights from the pooled patient-level data from three randomized controlled trials (IN-TIME, ECOST, TRUST). *Eur Heart J* 2017;**38**:1749–55.

22. Wilkoff BL, Williamson BD, Stern RS, Moore SL, Lu F, Lee SW *et al.* Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients. Results from the PREPARE (primary prevention parameters evaluation) study. *J Am Coll Cardiol* 2008;**52**:541–50.

23. Gasparini M, Proclemer A, Klersy C, Kloppe A, Lunati M, Ferrer JBM *et al.* Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the advance III randomized clinical trial. *JAMA* 2013;**309**:1903–11.

24. Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP *et al.* Reduction in inappropriate therapy and mortality through ICD programming. *N Engl J Med* 2012;**367**:2275–83.