**Impact of remote monitoring on clinical outcomes for patients with heart failure and atrial fibrillation: Results from the REM-HF trial.**

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**Abstract (≤250 words)**

**Aims:** Studies of remote monitoring (RM) in heart failure (HF) speculate that patients with atrial fibrillation (AF) derive the greatest benefit. We compared the impact of RM versus usual care (UC) on clinical outcomes for patients with and without AF enrolled in the Remote Management of Heart Failure Using Implanted Electronic Devices (REM-HF) trial.

**Methods and Results:** Rhythm status was available for 1561 patients (94.6%). Three categories were defined based on total AF duration during the first year of follow-up: i) no AF (n=1211, 77.6%), ii) paroxysmal AF (≥6 minutes to ≤7 days; n=92, 5.9%), and iii) persistent (>7 days; n=258, 16.5%). Clinical activity, mortality, and hospitalisation rates were compared between treatment strategies for each group.RM resulted in a greater volume of clinical activity in patients with any AF, versus no AF, with the highest per-patient intervention required for patients with persistent AF. During 2.8±0.8 years’ follow-up,RM was not associated with a reduction in all-cause or cardiovascular mortality for patients with AF. However, in patients with persistent AF, RM conferred an increased risk of recurrent cardiovascular (HR 1.40, 95%CI 1.06-1.85, p=0.018) and HF-related (HR 2.05, 95%CI 1.14-3.69, p=0.016) hospitalisations.

**Conclusion:** In patients with HF and a CIED, RM generated greater clinical activity for patients with AF, with no associated reduction in mortality, and conversely, greater risk of cardiovascular hospitalisation amongst patients with persistent AF. RM strategies may vary in their capability to guide HF management; modified approaches may be needed to improve outcomes for HF patients with AF.

**Key words:** Atrial fibrillation, remote monitoring, heart failure, cardiac implantable electronic device

**Introduction**

Patients with chronic heart failure (HF) experience high rates of hospitalisation, which may accelerate HF progression and worsen prognosis1, 2. Hospitalisations also generate substantial healthcare costs and impair quality of life, thus reducing hospital admissions has become an important aim of HF management. Contemporary remote monitoring (RM) strategies wirelessly transfer physiological data to healthcare providers, enabling more frequent and sensitive assessment of a patient’s clinical status, and proactive intervention for early signs of HF decompensation. In theory, this may avert hospitalisation and reduce mortality. In practice, however, trials employing RM in chronic HF management have shown mixed results.

In patients with HF and a cardiac implanted electronic device (CIED), multiparameter RM in the Inﬂuence of Home Monitoring on Mortality and Morbidity in HF Patients with Impaired left Ventricular Function (IN-TIME) trial led to a reduction in a composite clinical score (incorporating death, HF hospitalisation, worsened NYHA functional class or worsened self-reported overall condition), but did not specifically reduce the number of hospital admissions for worsening HF3. By contrast, multiparameter RM employed in the Remote Management of Heart Failure Using Implanted Electronic Devices (REM-HF) trial, demonstrated no reduction in in mortality CV hospitalisations as a composite primary endpoint or secondary (individual) outcomes. To date, only single-parameter invasive pulmonary artery pressure monitoring, by a dedicated implanted device, has been proven to reduce HF hospitalisation rates4, whilst several other studies have demonstrated feasibility of device-based RM, but inconsistent benefits over standard HF care. In view of these discrepancies, there remains a need to identify (and match) the most appropriate patients, key RM variable(s), and early intervention(s) that will give rise to improved HF outcomes with this approach.

With this in mind, the amount and type of atrial tachyarrhythmia (predominantly atrial fibrillation [AF]) can be accurately quantified, and has been linked to HF hospitalisation risk5, 6. AF is also an important cause of stroke, inappropriate shocks, and reduced biventricular pacing, which limits the efficacy of cardiac resynchronisation therapy in HF. Early detection of AF with RM affords the opportunity to initiate anticoagulation, where appropriate, and optimise rate or rhythm control therapies, that may pre-empt stroke or AF-related HF decompensation. This was speculated as a key mechanism of benefit in the IN-TIME trial, where, on subgroup analysis, RM primarily improved outcomes for HF patients with a history of AF3, although this effect was driven by a reduction in all-cause mortality, with no rhythm-specific change in hospitalisation risk.

In the present study we aimed to verify whether a similar (and selective) reduction in mortality would be observed amongst patients with AF who were enrolled in the REM-HF trial7, as compared to patients in sinus rhythm. Secondly, we examined whether a reduction in hospitalisation risk may, in fact, become evident when all (i.e. recurrent) hospitalisations were considered, beyond the first event, and finally, we explored the potential mechanism(s) of benefit for RM unique to patients with AF. Specifically, we hypothesised that RM would prompt a greater volume and/or different patterns of clinical activity for patients with HF and AF, and that this change in activity would correspond to reduced rates of cardiovascular (CV) hospitalisation and mortality.

**Methods**

The design8 and results9 of the REM-HF trial have been reported previously. Briefly, 1650 patients with stable HFrEF (NYHA class II-IV) and a CIED implanted at least 6 months9, were randomized 1:1 to receive UC or management informed by active RM. The latter comprised weekly downloads of CIED-detected data including information regarding device function, type and episodes of arrhythmia, heart rate variability, activity levels, and thoracic impedance. Where necessary, changes in therapy were made with physician support and according to agreed operational RM care pathways, which may include planned hospitalisations (Supplemental Methods)8. The primary endpoint was a composite of death or unplanned hospitalisation due to a cardiovascular (CV) cause, and was not different between UC or RM groups9. All patients participating in the trial provided written informed consent and the trial was approved by independent ethics committees at each participating site.

In the current pre-specified analysis, all device-detected atrial high rate episodes within the first year of follow-up were captured (for patients with an intra-atrial lead) and summated to obtain an overall atrial tachyarrhythmia burden. Where rhythm data were unavailable from remote transmission, and for patients in the usual care arm, additional data were obtained from routine (6-monthly) in-person CIED interrogation. Individual episodes of arrhythmia were not exhaustively adjudicated, however, intra-atrial electrograms have been shown to correlate well with surface electrocardiographic documentation of AF10, and are henceforth referred to as AF. Three mutually exclusive rhythm groups were defined based on the duration of AF and in keeping with recognised AF classification11: (1) no device-detected AF, (2) paroxysmal device-detected AF, which incorporated subclinical AF (≥6 minutes and ≤24hours) and paroxysmal AF (>24hours to ≤7 days), and (3) continuous AF which incorporated persistent AF (>7 days to <1 year) and longstanding persistent AF (≥1 year; i.e. AF continuously present throughout the duration of monitoring). Patients who progressed from paroxysmal to persistent forms of AF during the first year of follow-up were classified as the latter. Furthermore, as rhythm status beyond 1 year and patient and physician decision-making regarding the pursuit of rhythm control were unavailable to REM-HF investigators, patients with a clinical categorisation of permanent AF could not be reliably distinguished and were therefore classified as having persistent AF for this analysis.

*Statistical analysis*

Patient characteristics and RM activities were compared between rhythm categories using the Chi-squared goodness of fit (categorical variables), one-way analysis of variance (continuous variables) or Wilcoxon rank-sum/Kruskal-Wallis tests (for non-normally distributed data). Categorical variables are reported as frequency (%), continuous variables as mean (SD) or median (LQ-UQ). Rates of death and hospitalisation were calculated from the total number of events divided by person-years at risk.

Cox proportional hazard modelling was used to determine the effect of treatment strategy on the risk of death and unplanned hospitalisation (as outcome measures), and effect modification by rhythm was assessed using the log partial likelihood ratio test. Stratified analyses, based on rhythm groups, were then performed to compare the effects of RM versus usual care on the risk of death and unplanned hospitalisation for each group. In each model, the proportional hazard assumption was checked using the scaled Schoenfeld residuals and found to be valid12. The effect of treatment strategy on the risk of first CV or HF-related hospitalisation was assessed using competing risks regression, based on Fine and Gray’s proportional subhazards model, with death assigned as a competing risk13. Prentice, Williams and Peterson models (total time method; PWP-TT) were used to examine the relationship between treatment strategy and recurrent CV or HF-related hospitalisation, with the time to each hospitalisation measured from the randomisation date. Patients were censored at time of death or last clinical follow-up. Complete case analysis was used in all modelling; a sensitivity analysis was performed with follow-up data truncated at ≤5 hospitalisations for improved stability of hazard ratio estimates. p-values are reported as two-sided with significance at p<0.05. Analyses were conducted with STATA version 15 (StataCorp LP, TX, USA).

**Results**

*Patient characteristics*

CIED-detected AF data were available for 1561 patients (94.6% of the REM-HF cohort). Many of the remaining 89 patients did not have an intra-atrial lead to enable reliable classification of AF. Baseline characteristics for patients with and without rhythm data were largely similar, with the exception of fewer implanted ICDs and greater proportion of CRT-P devices (Supplemental Table 1).

In the first year of follow-up, 71 (4.5%) patients were identified to have subclinical AF, 21 (1.3%) patients had paroxysmal AF, and 258 patients (16.5%) had persistent AF or LSPAF. Due to the low number of patients with subclinical and paroxysmal AF, these classifications were combined into a single category. AF was a new finding in 61% patients with paroxysmal AF and 20% of patients with persistent AF. Increasing AF burden (i.e. no AF<paroxysmal AF<persistent AF) was associated with more advanced age and NYHA class (**Table 1**). Comorbidities were equally distributed between rhythm groups, and average CHA2DS2VASc scores similar. Oral anticoagulants, loop diuretics, and digoxin were more commonly used, while aspirin and antiarrhythmic drugs (typically amiodarone) were less commonly used by patients with persistent AF versus other groups at baseline. Use of other medications was similar between rhythm groups.

Atrial fibrillation was equally represented in RM and UC treatment arms (22.7% RM vs 22.1% UC, p=0.780). Additionally, within each rhythm group, baseline characteristics were mostly similar between patients randomised to RM versus UC (**Supplemental table 1**). In the RM arm, most patients transmitted data for at least 75% of weeks in the study (**Table 1**).

*Clinical activity*

For patients randomised to RM, all outpatient clinical actions, not resulting in hospitalisation, were recorded during the trial. Amongst patients CIED-detected AF data in the RM arm (n=797), 5500 actions were recorded, over 3514 occasions, for 595 (74.7%) individuals in response to remote transmissions. These actions included all elective patient contact, clinical discussions, and advice given (**Figure 1**). Planned and unplanned hospitalisations were considered separately (see below). The median [LQ-UQ] number of outpatient clinical actions per patient-year of follow-up was significantly greater for patients with any AF (2.8 [0.8-6.5]) versus no AF (1.0 [0-3.3]; p<0.0005). Patients with persistent AF generated the greatest volume of outpatient activity per patient-year with respect to changes in medication and referral for additional in-person clinical review, although a marginally greater proportion of patients with paroxysmal AF were contacted and discussed with a clinician (**Figure 1, Supplemental Table 2**).

For all patients, irrespective of treatment allocation, all planned and unplanned hospitalisations were recorded during the trial. A total of 161 (10.3%) patients had 198 planned hospitalisations. Patients with paroxysmal AF were most likely to have a planned hospitalisation, followed by those with persistent AF and no AF, respectively (**Figure 2**). Irrespective of rhythm, more patients in the RM arm had a planned hospitalisation than patients receiving usual care, although the absolute difference between RM and usual care, was greatest for patients with paroxysmal AF (**Figure 2**).

Most planned hospitalisations were for a primary CV reason (64.6%), with only a small proportion of these designated as being primarily for AF management (15/198 hospitalisations [7.6%] in 14 patients. These included 2 hospitalisations for elective direct current cardioversion (n=1 RM, n=1 usual care), 3 scheduled procedure for AF/flutter ablation (n=1 RM, n=2 usual care), 9 scheduled procedures for atrioventricular node ablation (n=5 RM, n=4 usual care), and 1 hospitalisation for placement of a left atrial appendage occlusion device (n=1 usual care).

*Mortality*

Patients were followed up for a mean (SD) of 2.8 (0.8) years. In total, 252 patients (16.1%) died, resulting in a mortality rate of 5.9, 2.2, and 6.6 per 100 person-years at risk, for patients with no AF, paroxysmal AF and persistent AF respectively. RM was not associated with a reduction in all-cause mortality for the overall cohort (HR 0.88, 95%CI 0.69-1.12), however, effect modification by rhythm status was statistically significant (p value for rhythm interaction term=0.0006). On rhythm-stratified analyses, RM was associated with a slightly lower risk of death for patients with no AF, as compared with usual care (**Figure 3A**), which was statistically significant after multivariable adjustment (**Figure 4**). However, there was no survival benefit observed with RM for patients with paroxysmal or persistent AF. Moreover, after multivariable adjustment, patients with persistent AF in the RM arm exhibited a greater risk of all-cause mortality, as compared with usual care (**Figure 4**).

Two hundred and two deaths (80.2%) were attributed to a CV cause. The CV mortality rate was 4.7, 2.2, and 5.5 per 100 person-years at risk in patients with no AF, paroxysmal AF and persistent AF respectively. As for all-cause mortality, there was a significant interaction with rhythm status for the effect of treatment strategy on CV mortality (p=0.023). However, on rhythm-stratified analyses, no statistically significant difference was observed for the effect of RM on CV mortality between rhythm groups (**Figure 4**).

*Unplanned hospitalisations*

Overall, 789 patients (50.5%) had 1862 unplanned hospitalisations (median 2 per person, LQ-UQ 1-3). Most unplanned hospitalisations were due to a primary CV cause, from which worsening HF accounted for 43% (**Supplemental Table 3**).The overall unplanned CV hospitalisation rate was 14.8, 17.0, and 22.6 per 100 person-years at risk in patients with no AF, paroxysmal AF and persistent AF respectively, and the rate of unplanned HF-related hospitalisation: 6.9, 5.7, and 9.8 per 100 person-years at risk. When the time to the first CV or HF-related unplanned hospitalisation was assessed, there was no significant benefit of RM versus UC on hospitalisation rate for any rhythm group (**Figure 4**). However, when all unplanned hospitalisation events during trial follow-up were considered, a detrimental effect of RM, as compared with usual care, became apparent for patients with persistent AF, with an increased risk of recurrent CV and HF-related hospitalisations observed, even after accounting for death as a competing risk (**Figure 3B-C**) and relevant baseline characteristics (**Figure 4***).* For patients with paroxysmal AF and no AF, there was no difference in the risk of CV or HF-related hospitalisation (as a first or recurrent event) with RM versus UC (**Figure 3**).

*Sensitivity analyses*

A sensitivity analysis in which patients with any prior history of AF or atrial flutter (n=638, 41%) were excluded, was generally underpowered to detect a rhythm-specific effect of RM but still showed a protective effect of RM for patients with no AF, with regards to all-cause mortality (**Supplemental Figure 1**). A less restricted analysis, whereby only those patients who had previously undergone an ablation procedure for AF or flutter (n= 108, 6.9%), were excluded, did not alter the direction of the relationships observed in the main analysis (**Supplemental Figure 2**).

Secondly, because the risk of all-cause mortality and unplanned hospitalisation varied widely for patients with paroxysmal AF, i.e. the observed 95% confidence interval ranged from a 94% decreased risk of all-cause mortality with RM up to a 162% increased mortality risk (**Figure 4**), given our statistical assumptions, we explored the impact of varying the definition of paroxysmal AF. When paroxysmal AF was defined as a cumulative AF burden of up to 3 months (n=109, **Supplemental Figure 3**) or 6 months (n=113, **Supplemental Figure 4**) in duration, over the first year of follow-up, relatively few patients switched rhythm category. There was no marked change in the association between RM and mortality for any rhythm group, and the association between persistent AF and HF hospitalisation became stronger. Reclassifying patients with AF ≤24 hours in duration as ‘no CIED-detected AF (**Supplemental Figure 5**), or only including patients with a CRT device (i.e. excluding patients with an ICD alone; **Supplemental Figure 6**), did not alter the trends observed in this study.

Finally, when the dataset was truncated after the fifth hospitalisation (n=103 CV hospitalisations excluded), the positive association between RM and HF-related hospitalisations for patients with persistent AF remained statistically significant (HR 1.84, 95%CI 1.07-3.17, p=0.027), while the association with CV hospitalisations was borderline significant (HR 1.32, 95%CI 1.00-1.75, p=0.054).

**Discussion**

In this ancillary analysis of the REM-HF trial, CIED-detected AF was present in 22% of the study cohort. When compared to patients in sinus rhythm, patients with CIED-detected AF generated a greater volume of clinical activity in response to RM-received data. Importantly, however, this increase in physician-initiated activity did not directly translate into better outcomes. Rather, for patients with persistent AF, the use of RM to guide HF management was associated with an increased risk of all-cause mortality and a higher rate of emergency CV hospitalisation, versus usual care, with most hospitalisations due to worsening HF.

*Remote monitoring, atrial fibrillation and clinical activity*

Successful implementation of any RM strategy requires selection of the most appropriate monitoring parameter(s) for the population under study. In the implant-based IN-TIME trial3, and to some extent the telemonitoring-based CONNECT trial14, atrial tachyarrhythmias (mostly AF) were reported as the RM parameter that most often led to patient contact. Our data corroborate these findings, showing that patients with AF, overall, required a greater number of clinical actions across all domains. In particular, patients with paroxysmal AF were contacted, discussed and hospitalised (as a planned admission) more frequently than for any other rhythm group, and in 61% of cases paroxysmal AF was a new diagnosis, suggesting heightened vigilance for new-onset arrhythmias. Importantly, however, the data collected in REM-HF and IN-TIME did not allow for a precise correlation between alerts, physicians’ responses and outcomes, and the significance and management of short-lived episodes of AF remains unclear.

Moreover, in the current study, a crude estimate of overall health resource utilisation (including outpatient actions, planned and unplanned hospitalisations) showed the greatest per-patient intervention requirements were in patients with persistent rather than paroxysmal AF, many of whom would already have a diagnosis of AF, or persistent AF would be clinically detectable without RM. This is not entirely unexpected, owing to a generally sicker patient population having persistent versus paroxysmal (or no) AF, and the absolute differences in number of clinical actions were not large. Nevertheless, these data question the incremental value of more sensitive AF detection for chronic HF management, and in patients with persistent AF, other diagnostic parameters, besides AF detection, more likely drove clinical activity, such as high resting ventricular rate, lower biventricular pacing percentage, or increased intrathoracic impedance.

A second important consideration for integrating RM into chronic HF management is the frequency of scheduled RM transmissions15. The IN-TIME trial employed daily checks of RM data (on all working days), with additional programmed ‘alerts’ by a central monitoring unit. By contrast, REM-HF utilised weekly data checks, without dedicated alerts for HF management. As HF decompensation typically develops over several days or weeks, it is expected that detection and pre-emptive intervention would be possible with either approach. However, we observed more frequent primary rhythm-related hospitalisations in patients with AF, and sudden-onset episodes of tachy- or brady-arrhythmia may be more common in patients with AF than sinus rhythm, potentially precipitating HF decompensation within a short(er) timeframe. Daily RM transmissions, if accompanied by a shorter time between medical event and patient contact, may preferentially benefit patients with AF and be one explanation for the different outcomes in the IN-TIME3 and REM-HF7 trials.

Thus, while our data confirm that CIED-detected AF identifies a subgroup of patients with more advanced HF (and more deranged parameters), who would theoretically derive benefit from RM-guided care, further clarification is needed regarding which ‘actionable’ parameters and frequency of RM transmissions will most efficiently improve outcomes for this group.

*Remote monitoring, atrial fibrillation and mortality*

In the present study, RM was not associated with a reduction in all-cause or CV mortality for patients with paroxysmal or persistent AF. Conversely, a potential increase in all-cause mortality was observed for patients with persistent AF, and a reduction in all-cause mortality was observed for patients in sinus rhythm. Although this is a subgroup (and post hoc) analysis, the findings are in direct contrast to a subgroup analysis from the IN-TIME trial, where the survival benefit was predominantly seen amongst patients with a history of AF3. It should be highlighted that neither REM-HF nor IN-TIME were powered to demonstrate a survival advantage, and REM-HF did not demonstrate an overall reduction in mortality (as a secondary endpoint)9. Nevertheless, death and hospitalisation rates, stratified by heart rhythm, have not been reported for IN-TIME and the discrepancy between these two trial outcomes is interesting.

One potential explanation may relate to differences in the patient population studied. Enrolled patient characteristics from the IN-TIME trial point towards a marginally more advanced HF cohort as compared to REM-HF, including a lower mean EF (26% versus 30%), greater proportion of patients in NYHA class III (57% versus 30%), and greater diuretic requirement (>90% versus 77%). Possibly as a result, 1-year all-cause mortality in the usual care group was 8.7% in IN-TIME versus 4.8% in REM-HF. As patients with NYHA class III symptoms likely have more deranged RM parameters than patients with milder degrees of HF, RM may show a greater benefit in more severe HF, due to greater scope for RM-guided intervention.

Patients with permanent AF were ineligible for enrolment in IN-TIME, but this was not an exclusion criterion in REM-HF, and a greater proportion of patients with permanent AF may have mitigate the benefit(s) of RM. For example, patients with paroxysmal AF, despite less severe HF, could derive greater prognostic benefit from RM, by starting anticoagulant therapy, improving rate control or restoring sinus rhythm. These therapeutic options may have already been initiated or exhausted in the treatment of patients with persistent or permanent AF. More patients with paroxysmal AF were commenced on anticoagulation in the RM arm than usual care, during the trial, and the observed difference in mortality risk with RM, for patients with paroxysmal AF ranged widely, from a 94% decreased risk of death to a 162% increased risk, given our statistical assumptions16. Finally, the duration of follow-up may also be a relevant consideration. REM-HF had a longer follow-up duration than IN-TIME (mean 33±10 months versus mean ~28±3 months), which may have diminished a survival benefit for RM in patients with AF and concurrently revealed an emerging benefit for patients in sinus rhythm. The Kaplan Meier survival curves comparing RM and usual care more prominently diverged after 30 months’ follow-up, suggesting a potentially limited window for therapeutic gain using RM in this subgroup.

Even so, it remains difficult to explain why RM conferred an increase in mortality versus usual care for patients with persistent AF in this analysis. Some therapies have a poorer evidence-base in the setting of AF than for sinus rhythm (e.g. beta-blockers17, CRT18), and aggressive therapy may subject patients with AF to adverse effects, e.g. hypotension, in the absence of strong prognostic benefit. Nevertheless, this is speculative and, to date, clinical trials of RM, including REM-HF, have not identified safety concerns with respect to their primary and secondary endpoints3, 9, 19. Therefore, this subgroup finding requires further verification.

*Remote monitoring, atrial fibrillation and unplanned hospitalisation*

Studies to date suggest that different RM platforms may vary in their capability to support the management of chronic HF. For example, in the CHAMPION trial, daily transmission of invasive pulmonary artery pressure data, and the ensuing clinical response, led to fewer HF hospitalisations, however a number of other device-based RM strategies have been unable to achieve the same result3, 20-22. Curiously, even the IN-TIME trial reported no change in hospital admissions with RM, in spite of a reduction in mortality3. Given that only the first hospitalisation event was considered in the IN-TIME primary composite endpoint, and the impact of a RM strategy on recurrent hospitalisations may be a more relevant marker of its value in chronic HF management, we took advantage of adjudicated outcomes in REM-HF to examine all unplanned hospitalisation events during follow-up. In doing so, there was still no reduction in admissions for any rhythm group undergoing RM, and paradoxically, RM was associated with an increase in unplanned CV and HF hospitalisations for patients with persistent AF.

The reasons for this outcome are not immediately clear. A similar finding was observed in the Diagnostic Outcome Trial in Heart Failure (DOT-HF) trial, where the total number of hospitalisations was seen to increase when more diagnostic information (in the form of patient audible alerts) became available23. In the current study, rates of hospitalisation due to worsening HF were higher in patients receiving RM versus UC (8.0 versus 12.8 per 100 patient-years at risk) for the group with persistent AF, suggesting that these admissions were not driven by unnecessary vigilance, i.e. false positive alerts in the absence of signs of HF, which was speculated as a cause in the DOT-HF trial23.

Given that overall healthcare utilisation (including outpatient visits and hospital admissions) was also seen to increase with RM in patients with AF, future RM trials will need to investigate whether rhythm-specific parameters or thresholds for RM-based intervention may be needed, as well as identify more effective disease management pathways when AF and HF co-exist.

*Limitations*

Although this analysis of RM outcomes by rhythm status was prespecified in the REM-HF trial protocol, nevertheless, the overall number of patients with AF was relatively low and the study was not powered for rhythm-stratified analyses, therefore our findings should be considered hypothesis-generating only. Individual episodes of device-detected atrial tachyarrhythmia were not routinely adjudicated, and therefore a proportion of episodes may be false positive, including atrial flutter, atrial tachycardia or artefact; although exclusion of episodes of less than 5 minutes is suggested to eliminate most over-sensing10. Only AF duration during the first year of follow-up was available, however this represents a longer period of surveillance than recent studies of AF burden24. Progression from paroxysmal to persistent AF during the first year of monitoring was classified as the latter at the point of data collection, and rhythm status at the end of follow-up was not collected, therefore the number of patients who may have transitioned from one rhythm status to another during the trial is not known. Decisions regarding AF management were not separately recorded during REM-HF, which was primarily designed to examine HF-related management and outcomes. Although a number of patients with no CIED-detected AF had previously undergone an ablation procedure for AF or atrial flutter, this would serve to minimise the difference in risk between groups (i.e. bias the result towards no difference between groups where AF was present or absent). When these patients were excluded in a sensitivity analysis, the overall associations observed were unchanged. For analysis of recurrent hospitalisations, only baseline data regarding comorbidities were available and therefore these were treated as time-invariant. The PWP-TT model does not account for death as a competing risk. As hospitalisations in patients with HF have been associated with increased risk of future admission, the stratified baseline hazard utilised in the PWP-TT model, was selected as the most appropriate modelling technique.

**Conclusions**

In patients with HF and a CIED, the presence of AF was associated with a greater requirement for RM-prompted activity as compared to patients with no AF. This increase in physician-initiated activity did not translate into better outcomes. Rather, for patients with persistent AF, a strategy of RM using weekly alerts was associated with an increased risk of all-cause mortality and unplanned CV hospitalisation versus usual care. These findings highlight uncertainty as to whether more sensitive detection of AF is a significant or common mechanism of benefit for device-based RM in a contemporary HF population, and perhaps suggest that modified approaches or distinct RM platforms may be necessary to realise the benefits of RM for the management of patients with chronic HF and persistent AF.

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**Conflicts of interest:**

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**Figure Legends**

**Figure 1.** Outpatient clinical actions taken in response to remote monitoring. *AF classification refers to the total duration of AF in the first year of follow-up.*

**Figure 2.** Hospitalisations during the REM-HF trial. *AF classification refers to the total duration of AF in the first year of follow-up.*

**Figure 3.** Cumulative incidence of (A) all-cause mortality, (B) cardiovascular hospitalisation, and (C) heart-failure hospitalisation in patients with no AF or persistent AF, stratified by treatment arm. *Analyses of hospitalisation risk account for the competing risk of death.*

**Figure 4.** Comparison of treatment effects of remote monitoring (versus usual care) for clinical outcomes, stratified by rhythm group. *Hazard ratios displayed are adjusted for age, sex, device type, study site, systolic blood pressure.*

**Table 1.** Baseline characteristics according to atrial fibrillation burden at 1-year follow-up

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | No AF  (n=1211) | Paroxysmal AF (n=92) | Persistent AF  (n=258) | p-value |
| Age (y) | 68.9 ±10.3 | 69.0±9.8 | 72.1±9.1 | 0.04 |
| Male, n (%) | 1029 (85.0) | 77 (83.7) | 234 (90.7) | 0.047 |
| Systolic BP (mmHg) | 119.9±17.9 | 120.0±20.7 | 114.4±16.1 | 0.009 |
| Diastolic BP (mmHg) | 70.0±11.2 | 69.7±10.7 | 70.2±11.2 | 0.859 |
| Heart rate (bpm) | 67.7±10.0 | 69.4±10.4 | 70.9±9.8 | 0.813 |
| BMI (kg/m2) | 28.9±5.7 | 28.7±5.0 | 29.2±5.4 | 0.119 |
| NYHA, n (%)  II  III  IV | 862 (71.2)  347 (28.7)  2 (0.2) | 60 (65.2)  31 (33.7)  1 (1.1) | 167 (64.7)  91 (35.3)  0 | 0.05 |
| Type of CIED  ICD  CRT-D  CRT-P | 446 (36.8)  622 (51.4)  143 (11.8) | 26 (28.3)  55 (59.8)  11 (12.0) | 57 (22.1)  160 (62.0)  41 (15.9) | <0.0005 |
| Previous AF/flutter | 400 (33.0) | 36 (39.1) | 202 (79.5) | <0.0005 |
| Prior AF ablation, n (%) | 42 (3.5) | 7 (7.6) | 22 (8.6) | 0.001 |
| Prior A flutter ablation, n (%) | 22 (1.8) | 5 (5.4) | 10 (3.9) | 0.019 |
| Prior VT ablation, n (%) | 36 (3.0) | 8 (8.7) | 8 (3.1) | 0.013 |
| Hypertension, n (%) | 388 (32.2) | 37 (40.2) | 84 (33.1) | 0.286 |
| Prior MI, n (%) | 715 (59.4) | 55 (59.8) | 153 (60.2) | 0.968 |
| Prior CABG surgery, n (%) | 367 (30.5) | 34 (37.0) | 87 (34.3) | 0.250 |
| Prior PCI, n (%) | 306 (25.4) | 29 (31.5) | 52 (20.5) | 0.083 |
| Documented CAD, n (%) | 812 (67.4) | 64 (69.6) | 177 (69.7) | 0.728 |
| COPD, n (%) | 143 (11.9) | 7 (7.6) | 22 (8.7) | 0.182 |
| Prior stroke or TIA, n (%) | 161 (13.4) | 14 (15.2) | 40 (15.8) | 0.562 |
| Diabetes mellitus  I, n (%)  II, n (%)  II on medication | 13 (1.1)  293 (24.2)  205 (17.2) | 0  22 (23.0)  15 (16.5) | 1 (0.4)  81 (31.4)  52 (20.4) | 0.102  0.462 |
| Moderate to severe valve disease, n (%) | 50 (5.4) | 2 (2.9) | 11 (5.5) | 0.666 |
| LVEF (%) | 30.0±10.2 | 30.9±9.5 | 29.5±9.4 | 0.280 |
| CHA2DS2VASc score | 3.70±1.43 | 3.79±1.51 | 4.04±1.50 | 0.495 |
| *Medication at baseline* |  |  |  |  |
| Oral anticoagulant, n (%) | 432 (36.3) | 29 (31.9) | 189 (74.1) | <0.0005 |
| Aspirin, n (%) | 728 (61.2) | 59 (64.8) | 94 (36.9) | <0.0005 |
| ACEI, n (%) | 787 (66.1) | 58 (63.7) | 163 (63.9) | 0.738 |
| ARB, n (%) | 315 (26.5) | 27 (29.7) | 75 (29.4) | 0.541 |
| ACEI or ARB, n (%) | 1085 (89.6) | 83 (90.2) | 234 (90.7) | 0.861 |
| Beta-blockers, n (%) | 1064 (89.4) | 80 (87.9) | 234 (91.8) | 0.449 |
| Aldosterone antagonist, n (%) | 530 (44.5) | 41 (45.1) | 122 (47.8) | 0.629 |
| Loop diuretic, n (%) | 739 (62.1) | 56 (61.5) | 188 (73.7) | 0.002 |
| Other diuretic, n (%) | 155 (13.0) | 9 (9.9) | 42 (16.5) | 0.204 |
| Cardiac glycoside, n (%) | 152 (12.8) | 12 (13.2) | 85 (33.3) | <0.0005 |
| Anti-arrhythmic, n (%) | 234 (19.7) | 16 (17.6) | 31 (12.2) | 0.019 |
| *REM-HF treatment allocation* |  |  |  |  |
| Randomisation group  Remote monitoring, n (%)  Usual care, n (%) | 616 (50.9)  595 (49.1) | 57 (62.0)  35 (38.0) | 124 (48.1)  134 (51.9) | 0.070 |
| Proportion of patients in the RM arm with >75% transmitted data  6 months, n (%)  1 year, n (%)  2 years, n (%) | 487 (79.0)  473 (76.8)  429 (69.6) | 49 (86.0)  44 (77.2)  40 (70.2) | 99 (79.8)  97 (78.2)  94 (75.8) | 0.035  0.208  0.298 |

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CIED, cardiac implanted electronic device; COPD, chronic obstructive pulmonary disease; CRF, case record form; CRT-D, cardiac resynchronisation therapy – with defibrillator; CRT-P, cardiac resynchronisation therapy – with pacing only; LA, left atrial; LVEDD, left ventricular end diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic dimension; MI, myocardial infarction; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack; VT, ventricular tachycardia.