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ORIGINAL RESEARCH ARTICLE

# Heart failure patients with atrial fibrillation benefit from remote patient management: insights from the TIM-HF2 trial

Tina Stegmann[1*†], Kerstin Koehler[2†], Rolf Wachter[1], Volker Moeller[2], Samira Zeynalova[3], Friedrich Koehler[2†] and Ulrich Laufs[1†]

[1]*Clinic and Policlinic for Cardiology, University Hospital Leipzig, Liebigstraße 20, Leipzig, 04103, Germany;* [2]*Centre for Cardiovascular Telemedicine, Department of Cardiology and Angiology at Campus Mitte, Charité–Universitätsmedizin-Berlin, Berlin, Germany;* [3]*Institute for Medical Informatics, Statistics and Epidemiology, (IMISE), University of Leipzig, Leipzig, Germany*

## Abstract

**Aims** Atrial fibrillation (AF) is a frequent comorbidity in patients with heart failure (HF). HF patients with AF are characterized by high morbidity and increased risk of hospitalizations. We assessed the effects of remote patient management (RPM) in HF patients with AF compared with usual care (UC) in the TIM-HF2 trial.

**Methods and results** For this post-hoc analysis, AF status at randomization was assessed in 1537 patients with HF. The primary outcome was the percentage of days lost due to unplanned cardiovascular hospital admissions or death of any cause. Around 966 patients had sinus rhythm (SR) and 571 had AF. The analysis showed a significant interaction between heart rhythm and all-cause mortality (*P* for interaction = 0.001). AF patients had more days lost due to unplanned cardiovascular hospitalization than SR patients (7.53%, CI 6.01–9.05 vs. 4.90%, CI 3.98–5.82, ratio 1.54, *P* = 0.004) and higher all-cause mortality (11.9%, CI 9.4–14.9 vs. 8.5%, CI 6.8–10.4, HR 0.66, CI 0.47–0.94, *P* = 0.029). Patients with AF randomized to RPM had significantly less days lost due to unplanned cardiovascular hospital admissions or all-cause death (5.64%, CI 3.81–7.48) than patients with AF randomized to UC (9.37%, CI 6.98–11.76, ratio 0.60, *P* = 0.015). No difference was seen in SR patients (UC: 5.25%, CI 3.93–6.58, RPM: 4.55%, CI 3.27–5.83, ratio 0.87, *P* = 0.452). All-cause mortality in AF patients was reduced with 9.2% (CI 6.1–13.2) in the RPM group compared with 14.5% (CI 10.7–18.1) in the UC group (HR 0.60, CI 0.36–1.00, *P* = 0.050).

**Conclusions** For patients with atrial fibrillation at study entry, RPM was associated with increased days alive out of hospital. Our results identify HF patients with atrial fibrillation as a promising target population for RPM.

**Keywords** Remote patient management; Telemonitoring; Heart failure; Atrial fibrillation; Mortality; Personalized medicine

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**Correspondence to: Tina Stegmann, Clinic and Policlinic for Cardiology, University Hospital Leipzig, Liebigstraße 20, 04103 Leipzig, Germany. Tel: +49 341 9720972; Fax: +49 3419712688. Email: tina.stegmann@medizin.uni-leipzig.de*
*†T. Stegmann, K. Koehler, F. Koehler, and U. Laufs contributed equally*

## Introduction

Despite effective therapeutic strategies for patients with chronic heart failure (HF), the remaining risk for hospitalization and death is high.[1,2] About 2% of the adult population are affected by HF worldwide.[3] Timely detection of worsening of HF and early therapeutic interventions are therefore needed to prevent hospitalizations. In this context, the effects of telemedicine interventions were assessed for their potential to improve the outpatient care of patients with HF.[4–8] Current concepts pursue holistic ambulant care programs such as remote patient management (RPM). RPM includes telemonitoring and telemedical interventions, guideline-based ambulatory care, and patient education.[9] This theoretically enables a structured management, early detection of worsening disease, more rapid intervention, and improvement of patient self-empowerment.[9]

TIM-HF2 was a randomized controlled multicentre trial that reported reduced mortality and morbidity in patients with chronic HF by using non-invasive RPM.[10] For translation

of these findings into broader patient care, selection of patients who benefit most from allocation to RPM represents a key challenge.[11]

Atrial fibrillation (AF) is a frequent comorbidity in HF with increased mortality, hospitalizations and high morbidity.[12–15] AF patients are mostly older, have more comorbidities, and increased risk for stroke.[16,17] It is therefore conceivable that this high-risk group may have exceptional benefit from RPM. For example, close heart rate and rhythm control may reduce AF-related hospitalizations or prevent worsening of the disease. Findings of the IN-TIME study confirm these suggestions.[5] In their subgroup analysis, HF patients with AF were more likely to benefit from telemonitoring compared with patients without such a history. One speculated mechanism was more patient contact and early detection of AF due to telemonitoring. Other studies such as the REM-HF trial have not confirmed all of these observations.[18]

We therefore studied whether HF patients with AF at randomization may have increased benefit from non-invasive RPM as compared with patients with sinus rhythm (SR).

# Methods

## Study population

Details of the study design, randomization, procedures, data collection, and primary results of TIM-HF2 have been previously published (trial number: NCT01878630).[10,19] TIM-HF2 was a multicentred, randomized, controlled, and parallel-grouped study. The trial was conducted in Germany, and the patients were recruited from 200 sites, local and regional hospitals, the patient's general practitioner and local cardiologists. The study complied with the Declaration of Helsinki and the applicable laws and regulations. All patients provided written informed consent.

TIM-HF2 randomized patients with a history of hospitalization due to worsening HF within the last 12 months before randomisation and New York Heart Association (NYHA) functional class II or III and a left ventricular ejection fraction of 45% or lower (or if more than 45%, patients were being treated with oral diuretics). The patients were followed over 365 days.

Briefly, the following interventions were part of the RPM system: daily transmission of body weight, systolic and diastolic blood pressure, heart rate, analysis of the heart rhythm, peripheral capillary oxygen saturation, and self-rated health status.[10] The telemedical centre (TMC) was located at Charité–Universitätsmedizin Berlin. The TMC provided physician-led medical support and patient management 24 h a day, Monday to Sunday. A full description of the RPM system was reported previously.[19]

For this post-hoc analysis, only patients with confirmed SR or AF at randomization were included.

## Outcome

The primary outcome was the percentage of days lost due to unplanned cardiovascular hospitalizations or all-cause death. Key secondary outcomes were all-cause mortality, cardiovascular mortality, and quality of life. Both the primary and secondary outcomes were analysed first for patients in SR compared with patients with AF. Then patients with AF assigned to RPM or usual care (UC) and patients with SR assigned to RPM or UC were compared, respectively.

## Analysis of heart rhythm

To analyse the heart rhythm, each patient in the RPM and UC trial arm received a 12-lead electrocardiogram (ECG) at baseline and at the final visit from their attending physicians. The heart rhythm in the 12-lead ECG was reported in the case report form (CRF). In some patients, this information in the CRF was missing. In the RPM group, therefore, the first three ECGs from the daily RPM transmission were analysed, and the underlying rhythm was taken for analysis. For patients in the UC group, the reported heart rhythm from the last medical report prior to randomization was used. Patients were then stratified into patients with SR and patients with AF. For one patient from the UC group, no information about the heart rhythm at baseline was available; therefore, 1537 patients were included in the full-analysis set.

## Causes of death and hospital admissions

A clinical endpoint committee, masked to study group assignment, adjudicated all deaths and hospital admissions during the study period using prospectively defined criteria in the clinical endpoint committee charter.

## Pharmacotherapy and telemedical interventions

Patients in both groups were seen by their treating cardiologists at baseline and by their general practitioner or treating cardiologist at the final visit. At baseline and at the final visit, data from the current pharmacotherapy were collected in CRFs. Based on this information, the averages of ACE inhibitors, AT1-inhibitors, ß blockers, thiazides, loop diuretics, other diuretics, aldosterone antagonists, calcium antagonists, digitalis glycosides, antiarrhythmic drugs, vitamin K antagonists, and oral anticoagulation have been measured. Only patients with available data from CRF at baseline and final visit were included in the analysis. In the RPM group the number

of changes in cardiac pharmacotherapy and the number and duration of telephone calls with the patients were documented.

## Quality of life

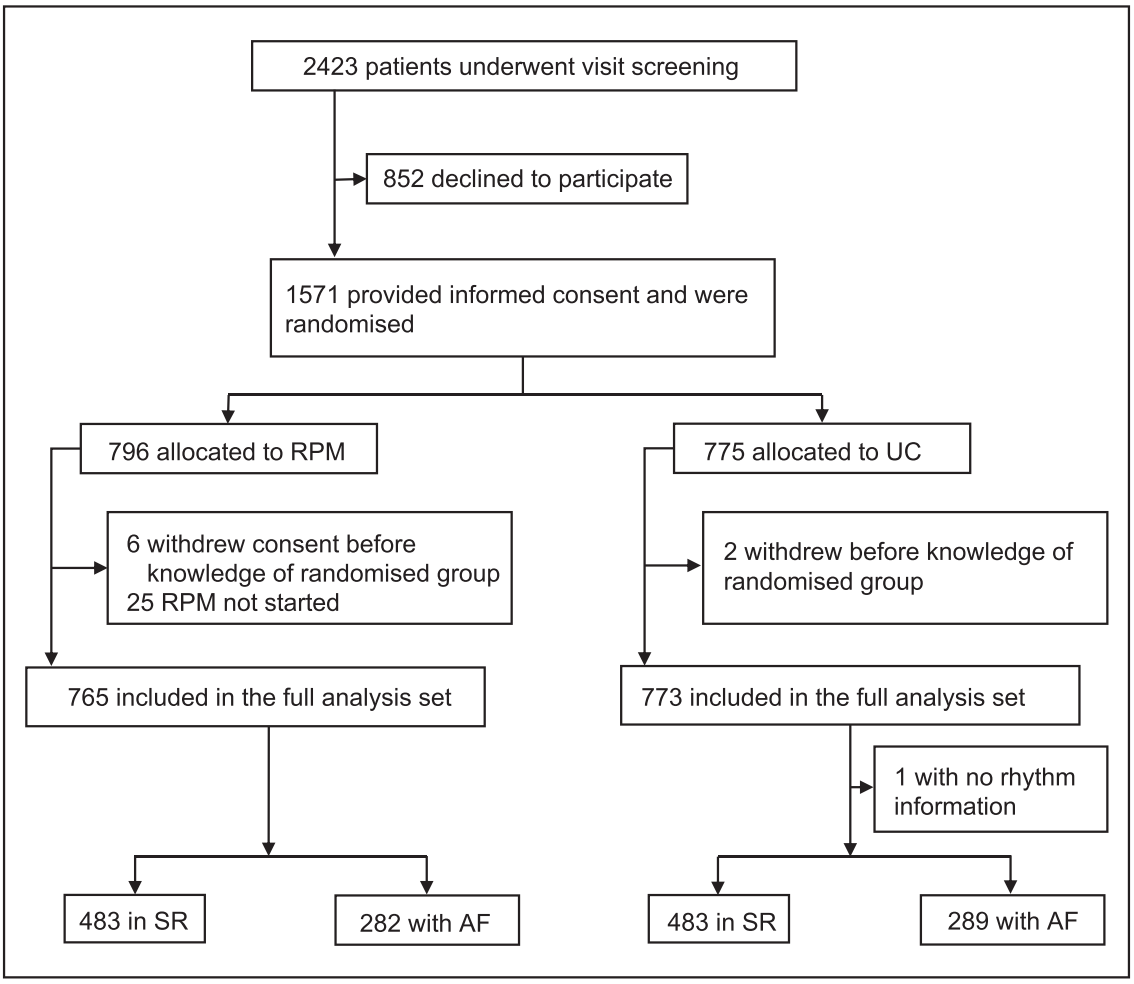
The Minnesota Living with Heart Failure Questionnaire (MLHFQ) was used to survey the quality of life of the HF patients at the start and the end of the study.[20] For the analysis, a global score was calculated for the baseline visit and the final visit in order to assess changes in the quality of life.

## Statistical analyses

Data analysis was performed using SPSS version 24 for Windows (IBM, Chicago, United States). For this post-hoc analysis, all patients within the full-analysis set were included. The full-analysis set was defined by all randomized patients who gave their written and signed consent. Baseline characteristics, stratified between patients in SR and patients with AF, were evaluated as number of patients (%) for categorical variables and continuous variables as mean ± standard deviation (SD) or median (25th, 75th interquartile ranges), depending on the distribution. Student's *t*-test or non-parametric tests (Man–Whitney *U*-test) were used for continuous variables. Categorical variables were analysed with the chi-square test or exact Fisher's test (where possible). For all analyses, statistical significance was set at $P < 0.05$ (two sided).

The primary outcome was evaluated during the individual-patient follow-up time (up to 28 days after the final study visit to a maximum of 393 days after randomization).[10] The averages of the percentage of days lost and 95% confidence intervals (CI) were calculated. All survival analyses

**FIGURE 1** Trial profile and the number of patients assigned to remote patient management or usual care with sinus rhythm or atrial fibrillation at randomisation which were included in the analysis.



were done on a time to first event basis. Survival analyses were performed by the Kaplan–Meier method, and differences between the curves were evaluated by log-rank test. Corresponding interaction between rhythm and the intervention was assessed by statistical interaction test. Specific hazard ratios (HR) for survival analyses were examined using the Cox-proportional regression model.

For all non-distributed variables analysing telemedical interventions and telephone calls, median values with interquartile ranges (25th, 75th) were used. Comparison of continuous variables were made by non-parametric tests (Man–Whitney *U*-test).

The change of the MLHFQ global score between patients in SR and patients with AF in both treatment groups was compared by ANCOVA model adjusting for the baseline value.

## Results

Of the 1538 patients in the analysis set, one participant with no information about the heart rhythm at randomization ($n$ = 1) was excluded, leaving 966 patients with SR (483 randomized to RPM and 483 to UC) and 571 with AF (282 randomized to RPM and 289 to UC, *Figure 1*). The characteristics of the patients at baseline are depicted in *Table 1*. Compared with patients in SR, patients with AF were older, had higher NT-proBNP values, lower glomerular filtration rate, and were more symptomatic (higher functional NYHA class, more peripheral oedema and more dyspnoea at exertion). They also suffered more often from hypertension and valvular heart disease. Patients with AF exhibited more co-morbidities than patients with SR [AF mean (SD): 4.29

**Table 1** Baseline demographics and clinical characteristics of the patients according to the heart rhythm

| | Atrial fibrillation ($n$ = 571) | | Sinus rhythm ($n$ = 966) | | |
|---|---|---|---|---|---|
| Characteristics | UC ($n$ = 289) | RPM ($n$ = 282) | UC ($n$ = 483) | RPM ($n$ = 483) | $P$ value[a] |
| Mean age, year (SD) | 73.8 (8.1) | 74.3 (8.0) | 68.4 (11.2) | 67.9 (11.2) | <0.001 |
| Female sex, no. (%) | 87 (30.1) | 89 (31.6) | 148 (30.6) | 143 (29.6) | 0.773 |
| Laboratory measurements | | | | | |
| NT-pro BNP (pg/ml) median (interquartile ranges) | 2,165 (1,329;4,174) | 2,152 (1,250;4,240) | 1,004 (407;2,241) | 1,035 (415;2,253) | <0.001 |
| GFR (ml/min per 1.73m$^2$) | | | | | <0.001 |
| mean (SD) | 64 (32) | 63 (32) | 73 (36) | 76 (40) | |
| < 60 | 142 | 152 | 197 | 180 | |
| > 60 | 133 | 125 | 259 | 284 | |
| Medical history, no. (%) | | | | | |
| Hypertension | 246 (85.1) | 239 (84.8) | 374 (77.4) | 383 (79.3) | 0.004 |
| Diabetes | 142 (49.1) | 134 (47.5) | 213 (44.1) | 213 (44.1) | 0.112 |
| Hyperlipidaemia | 155 (53.6) | 161 (57.1) | 260 (53.9) | 257 (53.2) | 0.784 |
| Coronary artery disease | 165 (57.1) | 165 (58.5) | 286 (59.2) | 277 (57.3) | 0.785 |
| Previous myocardial infarction | 79 (27.3) | 76 (27.0) | 135 (28.0) | 129 (26.7) | 0.403 |
| Peripheral artery diseases | 28 (9.7) | 24 (8.5) | 56 (11.6) | 57 (11.8) | 0.004 |
| Valvular heart disease | 165 (57.1) | 166 (58.9) | 233 (48.2) | 224 (46.5) | <0.001 |
| COPD | 61 (21.1) | 44 (15.6) | 77 (15.9) | 92 (19.0) | 0.679 |
| Previous stroke | 31 (10.7) | 37 (13.1) | 52 (10.8) | 45 (9.3) | 0.062 |
| Renal insufficiency | 167 (57.8) | 164 (58.2) | 248 (51.3) | 202 (41.9) | <0.001 |
| NYHA I | 1 (0.3) | 0 (0.0) | 7 (1.4) | 3 (0.6) | <0.001 |
| II | 137 (47.4) | 121 (42.9) | 258 (53.4) | 279 (57.8) | |
| III | 151 (52.2) | 160 (56.7) | 216 (44.7) | 199 (41.2) | |
| IV | 0 (0.0) | 1 (0.4) | 2 (0.4) | 2 (0.4) | |
| Peripheral oedema | 126 (43.8) | 132 (46.8) | 159 (32.9) | 142 (29.4) | <0.001 |
| Dyspnoea on exertion | 275 (95.2) | 264 (93.2) | 430 (89.0) | 433 (89.6) | <0.001 |
| Concomitant treatment | | | | | |
| ACE-inhibitors | 127 (46.9) | 139 (53.9) | 255 (56.5) | 254 (56.1) | 0.028 |
| AT1-inhibitors | 113 (46.9) | 139 (53.9) | 172 (39.7) | 154 (41.6) | 0.123 |
| ß blockers | 67 (93.7) | 255 (92.4) | 435 (93.3) | 438 (92.8) | 0.759 |
| Aldosterone antagonists | 131 (50.4) | 131 (52.2) | 247 (57.0) | 282 (63.4) | 0.001 |
| Thiazides | 42 (17.1) | 52 (21.7) | 66 (15.9) | 69 (16.8) | 0.175 |
| Loop diuretics | 271 (95.4) | 264 (95.7) | 427 (91.6) | 435 (92.4) | 0.010 |
| Other diuretics | 48 (19.1) | 35 (14.3) | 63 (14.9) | 64 (15.1) | 0.436 |
| Calcium antagonists | 67 (26.0) | 65 (26.2) | 112 (26.2) | 88 (20.8) | 0.296 |
| Digitalis glycosides | 101 (39.5) | 71 (41.3) | 28 (6.8) | 40 (9.6) | <0.001 |
| Antiarrhythmic drugs | 22 (8.8) | 27 (11.3) | 79 (18.9) | 74 (17.5) | <0.001 |
| Vitamin K antagonists | 159 (59.6) | 152 (57.6) | 102 (23.9) | 107 (24.9) | <0.001 |
| Other oral anticoagulants | 110 (42.0) | 108 (42.7) | 110 (26.3) | 103 (24.3) | <0.001 |

COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RPM, remote patient management; UC, Usual care.
One patient without the information about the heart rhythm at baseline was excluded from the analysis.
[a]Atrial fibrillation vs. Sinus rhythm.

**Table 2** Primary endpoint and all-cause mortality compared between patients in sinus rhythm and patients with atrial fibrillation

| | Atrial fibrillation ($n$ = 571) | Sinus rhythm ($n$ = 966) | Ratio (95% CI) | $P$ value |
|---|---|---|---|---|
| Percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause; average (95% CI) | 7.53% (6.01–9.05) | 4.90% (3.98–5.82) | 1.54[a] (0.94–2.13) | 0.004 |
| Days lost per year[b] (95% CI) | 27.5 (22.0–33.0) | 17.9 (14.5–21.2) | | |
| Number of patients with unplanned cardiovascular hospitalization or death of any cause | 249 (43.6%) | 306 (31.7%) | | |
| All-cause mortality[c] (95% CI) | 68 (11.9%) (9.4–14.9) | 82 (8.5%) (6.8–10.4) | 0.66[d] (0.47–0.94) | 0.029 |
| Cardiovascular mortality[c] (95% CI) | 46 (8.1%) (6.0–10.6) | 52 (5.4%) (4.0–7.0) | 0.65[d] (0.43–0.99) | 0.038 |

[a]Ratio of atrial fibrillation vs. sinus rhythm.
[b]Derived from the percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause: ((Percentage × 365)/100).
[c]Measured during individual patient follow-up time plus 28 days after the last study visit, to a maximum of 393 days.
[d]Hazard ratio.

(1.85), CI 4.14–4.43 vs. SR mean (SD): 3.96 (1.97), CI 3.84–4.08, $P$ = 0.004]. AF patients received more often anticoagulation and loop diuretics and less often mineralocorticoid receptor antagonists and ACE inhibitors.

## Outcomes

The analysis showed a significant interaction between the heart rhythm and the all-cause mortality ($P$ for interaction = 0.001). No significant interaction was seen for the primary endpoint (OR 1.2, n.s.). Patients with AF had more days lost due to unplanned cardiovascular hospital admissions or death of any cause compared with SR (AF: 7.53%, CI 6.01–9.05 vs. SR: 4.90%, CI 3.98–5.82; ratio 1.54, $P$ = 0.004, *Table 2*). Patients with AF lost 27.5 days (CI 22.0–33.0) and patients with SR lost 17.9 days (CI 14.5–21.2) per year. All-cause mortality was higher in patients with AF compared with SR (AF: 11.9%, CI 9.4–14.9 vs. SR: 8.5%, CI 6.8–10.4; HR 0.66, CI 0.47–0.94, $P$ = 0.029). The Kaplan–Meier curve for all-cause mortality is depicted in *Figure 2A*.

In a second step, the effect of assignment to RPM or UC was analysed in patients with AF and in those with SR (*Table 3*). The percentage of days lost due to unplanned cardiovascular hospital admissions or death of any cause in AF patients was 9.37% (CI 6.98–11.76) in the UC group and significantly reduced to 5.64% (CI 3.81–7.48) in the RPM group (ratio: 0.60; $P$ = 0.015). Patients with AF assigned to RPM lost an average of 20.6 days (CI 13.9–27.3) due to unplanned cardiovascular hospital admissions or death of any cause compared with 34.2 days (CI 25.5–42.9) per year in the UC group (*Table 3*). In contrast, for patients in SR, there was no significant difference in the percentage of days lost due to unplanned cardiovascular hospitalizations or death (*Table 3*; SR/UC: 5.25%, CI 3.93–6.58 vs. SR/RPM: 4.55%, CI 3.27–5.83, ratio: 0.87; $P$ = 0.45).

*Figure 2B* shows the Kaplan–Meier curves for patients in SR and AF in each arm of the trial. All-cause mortality was reduced from 14.5% (CI 10.7–18.1) in patients with AF in the UC group to 9.2% (CI 6.1–13.2) in the RPM group (*Table 3*; HR 0.60, CI 0.36–1.00; $P$ = 0.050). The all-cause death rate for patients in SR in the RPM group was 7.2% (CI 5.1–9.9) compared with 9.7% (CI 7.2–12.7) in the UC group (*Table 3*; HR 0.73; CI 0.46–1.14, $P$ = 0.166).

The cardiovascular mortality was equally reduced in all groups (*Table 3*, n.s).

## Causes of death

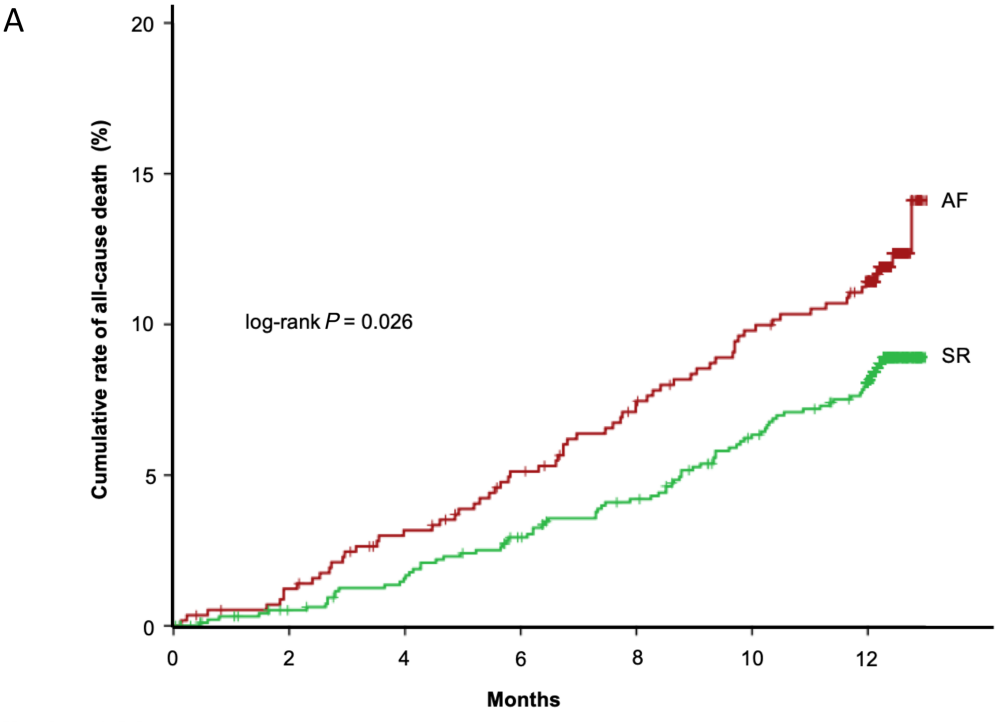
Around 142 patients' deaths were evaluated in this post-hoc analysis (Supporting Information, *Table S1*). Four patients in the UC group died due to stroke. Three of them had AF in their baseline ECG. No patient in the RPM group died due to stroke. Two patients with AF in the UC group died due to pulmonary embolism.

## Pharmacotherapy and telemedical interventions

*Table 4* depicts the information about the number of cardiac medication changes by a TMC physician as well as the number and duration of telephone calls during the trial. The recorded changes of cardiac medication were similar between AF and SR ($P$ = 0.16), according to the guidelines for the medical treatment of chronic HF.

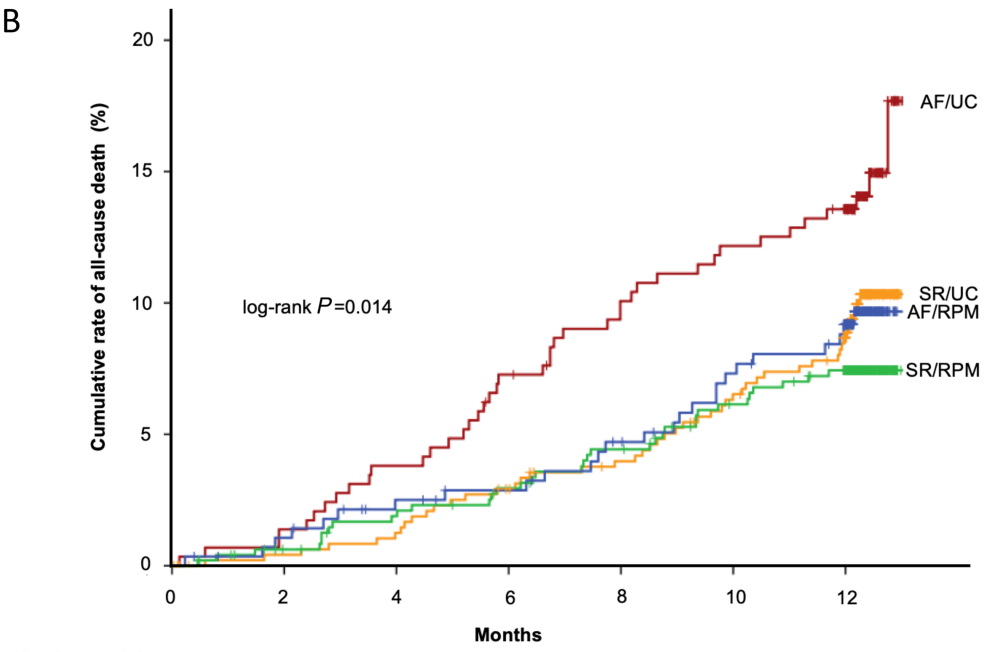
AF patients randomized to RPM received significantly more telephone contacts due to pharmacotherapy issues [*Table 4*, mean (SD); 2.6 (3.8)] than SR patients [1.8 (2.6); $P$ = 0.005]. The average lengths of the telephone calls due to pharmacotherapy issues (mean AF: 14 min 19 s vs. SR: 09 min 17 s, $P$ = 0.002) and the duration of the overall telephone calls during the whole follow-up period (mean AF: 02 h 36 min 58 s vs. SR: 02 h 11 min 36 s; $P$ < 0.001) were significantly higher for AF patients compared with SR patients (*Table 4*). The patients with AF had more frequent overall telephone contacts (all

**FIGURE 2** (A) Kaplan–Meier curve showing the cumulative rate of all-cause death in patients in sinus rhythm and patients with atrial fibrillation. (B) Kaplan–Meier curve depicting the cumulative rate of all-cause death in patients in sinus rhythm and patients with atrial fibrillation randomly allocated to remote patient management or to usual care.




**Number at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SR | 966 | 950 | 938 | 920 | 903 | 875 | 843 |
| AF | 571 | 562 | 547 | 532 | 515 | 500 | 483 |




**Number at risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| UC/SR | 483 | 477 | 473 | 462 | 453 | 439 | 423 |
| UC/AF | 289 | 285 | 278 | 267 | 257 | 251 | 244 |
| RPM/SR | 483 | 473 | 465 | 458 | 450 | 436 | 420 |
| RPM/AF | 282 | 277 | 269 | 265 | 258 | 249 | 239 |

**Table 3** Primary endpoint and key secondary outcomes compared between patients in sinus rhythm and patients with atrial fibrillation in the different trial arms

| | Atrial fibrillation ($n$ = 571) | | | | Sinus rhythm ($n$ = 966) | | | |
|---|---|---|---|---|---|---|---|---|
| | UC ($n$ = 289) | RPM ($n$ = 282) | Ratio (95% CI) | $P$ value | UC ($n$ = 483) | RPM ($n$ = 483) | Ratio (95% CI) | $P$ value |
| Percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause; average (95% CI) | 9.37% (6.98–11.76) | 5.64% (3.81–7.48) | 0.60[a] (0.25–0.95) | 0.015 | 5.25% (3.93–6.58) | 4.55% (3.27–5.83) | 0.87[a] (0.41–1.33) | 0.452 |
| Days lost per year[b] (95% CI) | 34.2 (25.5–42.9) | 20.6 (13.9–27.3) | | | 19.2 (14.4–24.0) | 16.6 (11.9–21.3) | | |
| Number of patients with unplanned cardiovascular hospitalization or death of any cause | 135 (46.71%) | 114 (40.43%) | | | 155 (32.09%) | 151 (31.26%) | | |
| All-cause mortality[c] (95% CI) | 42 (14.5%) (10.7–18.1) | 26 (9.2%) (6.1–13.2) | 0.60[d] (0.36–1.00) | 0.050 | 47 (9.7%) (7.2–12.7) | 35 (7.2%) (5.1–9.9) | 0.73[d] (0.46–1.14) | 0.166 |
| Cardiovascular mortality[c] (95% CI) | 28 (9.7%) (6.5–13.7) | 18 (6.4%) (3.8–9.9) | 0.64[d] (0.34–1.18) | 0.147 | 31 (6.4%) (4.4–9.0) | 21 (4.3%) (2.7–6.6) | 0.66[d] (0.38–1.17) | 0.154 |

[a]Ratio of atrial fibrillation vs. sinus rhythm.
[b]Derived from the percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause: ((Percentage × 365)/100).
[c]Measured during individual patient follow-up time plus 28 days after the last study visit, to a maximum of 393 days.
[d]Hazard ratio.


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**Table 4** Changes in cardiac pharmacotherapy and telephone calls by a physician of the telemedical health centre. Data are available from patients assigned to remote patient management. Changes in pharmacotherapy and telephone contacts are documented as numbers

| | Atrial fibrillation ($n$ = 282) | Sinus rhythm ($n$ = 483) | $P$ value |
|---|---|---|---|
| Telephone contacts due to pharmacotherapy[a] | 2.6 (3.8) | 1.8 (2.6) | 0.005 |
| Duration of telephone calls due to pharmacotherapy (in minutes)[a] | 14:19 (24:52) | 09:17 (15:09) | 0.002 |
| Telephone contacts overall[b] | 36 (26;46)[c] | 32 (26:44)[c] | 0.041 |
| Duration of overall telephone calls (in hours)[a] | 02:36:58 (01:38:26) | 2:11:36 (01:27:24) | <0.001 |
| Changes in cardiac pharmacotherapy by telemedicine physicians[a] | 4.0 (11.28) | 3.1 (9.1) | 0.162 |

[a]Mean (Standard deviation).
[b]Includes telephone contacts due to all pharmacotherapy issues and all other issues in hours.
[c]Median (Interquartile ranges).

matters included) with the TMC compared with patients in SR (*Table 4*, median contacts AF: 36 vs. SR: 32; $P$ = 0.041).

Supporting Information, *Figure S1* summarizes the distributions of the cardiac medication at the baseline and the final visit between patients in SR and AF. Overall, medication remained relatively stable throughout the trial in patients with SR and AF. Patients in SR had less vitamin K antagonists but more oral anticoagulations in the follow-up visit, which was the same in the UC and RPM groups. Oral anticoagulation in AF patients was relatively stable during the trial.

### Quality of life

The global score of the MLHFQ questionnaire at baseline (Supporting Information, Table S2) was numerically higher in AF patients (mean UC: 34.2 and RPM: 33.7) than in patients with SR (mean UC: 28.7 and RPM: 29.2), $P$ < 0.001 for AF vs. SR. This was similar at 12 months (mean AF/UC: 29.8, AF/RPM: 29.8, and SR/UC: 24.9, SR/RPM: 24.1; $P$ < 0.001 for AF vs. SR). There was no significant change from baseline global score to 12 months in both groups.

## Discussion

This retrospective analysis identifies patients with AF at study entry as a population of HF patients that shows high benefit from RPM in comparison with UC. For patients with AF, RPM was associated with fewer days lost due to unplanned cardiovascular hospitalizations or death of any cause. This effect was not observed in HF patients with SR. There was a significant interaction between the heart rhythm and the all-cause mortality.

The hypothesis of this post-hoc analysis was that patients with AF may especially benefit from RPM because of their higher morbidity. This hypothesis was supported by the IN-TIME study that showed a reduction of all-cause mortality and hospital admissions in patients with HF using implantable device-based (implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator) telemonitoring in addition to standard of care with a daily automatic data transmission compared with standard of care without telemonitoring. The post-hoc analysis of the IN-TIME study revealed a significant treatment benefit in patients with AF.[5] In the REM-HF trial, remote monitoring of patients with HF and a cardiac implanted electronic device was not associated with reduction in mortality in AF.[18] However, no analysis has previously compared the effects of comprehensive non-invasive RPM in patients with AF compared with SR.

In line with these and other previous reports, our analysis shows that patients with HF and AF are at higher risk of hospitalizations and death.[21,22] Our data identify a quantitatively very relevant beneficial effect of RPM in the AF population. Several factors are likely to contribute to this observation: Patients with AF represent a high-risk patient group with more co-morbidities. In agreement with the HF long-term registry of the European Society of Cardiology and other previous reports, the population of AF in TIM-HF2 was older, more likely to have hypertension and valvular heart disease.[16,23,24] They had a lower glomerular filtration rate, higher NT-pro BNP levels and more symptoms (worse NYHA functional class, peripheral oedema and dyspnoea at exertion). In addition, the number of non-cardiovascular deaths was similar in the AF/UC ($n$ = 13), SR/UC ($n$ = 16), and SR/RPM ($n$ = 13) groups but markedly reduced in the patients with AF that were provided with RPM ($n$ = 6). The more complex AF patients may therefore derive more benefit from RPM. Another interesting finding was that four patients in TIM-HF2 died due to stroke all of which were assigned to the UC group. Three of the patients had AF in their ECG at randomization. In contrast, no patient in the RPM group died due to stroke. Obviously, the number of strokes in TIM-HF2 is low, and future studies are needed to investigate a possible correlation. However, the data suggest that these complex patients at higher risk can be identified by the widely available ECG.

A further explanation for the positive effects of RPM in AF is that more time with telephone support by physicians of the TMC was spent with AF patients compared with patients in SR. The number and duration of contacts were recorded in TIM-HF2 and were significantly increased in the AF group. More frequent patient contact due to atrial arrhythmias were also observed in IN-TIME and REM-HF.[5,18]

However, all three studies were not powered for mortality analyses in patients with AF. In the IN-TIME and REM-HF trials, cardiac implanted electronic devices were used for remote monitoring. In contrast to a device-detected overall atrial tachyarrhythmia burden, we used the heart rhythm status by ECG at randomization. The most important difference, however, relates to the specific protocol of the RPM intervention that demonstrated reduction of morbidity and mortality in patients with HF.[10]

Other potential explanations for the benefit of RPM in AF may relate to differences in the pharmacotherapy. Studies such as the ESC long-term registry found that patients in SR are often better drug adjusted than patients with AF.[16] However, up-titration of guideline-recommended treatments or dosing of diuretics during the TIM-HF2 trial were similar in the AF and SR patients, both groups in the RPM trial arm received a similar number of cardiac medication changes by a TMC physician during the trial. Previous subgroup analyses of AF patients showed differences between groups with regard to RAAS inhibitors, neprilysin inhibition, beta blocker therapy, mineraloreceptor antagonists, and SGLT2-inhibition.[25–27] Differences in the pharmacotherapy therefore appear unlikely to explain the profound benefit for AF patients randomized to RPM.

Another important concept considering the pathophysiology of both diseases is that AF begets HF and vice versa. Patients with rate control show improved signs and symptoms of HF.[28,29] High cardiac filling pressures due to HF contribute to the development of AF.[28,29] This 'vicious cycle' can be therapeutically addressed, e.g. by pulmonary artery pressure guided management.[30]

In summary, several potential mechanisms may explain the positive effect of RPM in patients with AF. The results emphasize the importance of AF in HF and the potential of personalized medicine for patients with both coexisting conditions to reduce mortality and cardiovascular hospital admissions.

Including TIM-HF2, three prospective, randomized trials reported positive effects of telemedicine care in patients with HF.[5,6,10] Based on these data, patients with functional NYHA classes II and III and hospitalization due to HF in the last 12 months seem to benefit from RPM.[10,31] In order to translate these findings into daily care, strategies and additional criteria are required for patient profiling to select patients that are likely to benefit from these high-resource ambulant care programs. Potential selection criteria can include cardiac biomarkers such as NT-proBNP and MR-proADM.[32] This TIM-HF2 analysis identifies the potential of the baseline ECG as an additional and widely available selection criterion.

There are some limitations of the study. The history of AF was not a pre-specified subgroup. The reported findings are based on a post-hoc analysis and are therefore only hypothesis generating. The study was not powered for these subgroup analyses, which is the main reason for the non-significant but remarkable results on all-cause mortality ($P$ = 0.050). The changes in pharmacotherapy in the control groups were documented in the CRF but not confirmed otherwise. Patients who developed AF during the study were not considered in these analyses. The RPM in the TIM-HF2 trial was designed for the German health-care system, and the applicability with regard to other health care systems and other ethnicities needs to be tested.

In conclusion, this post-hoc analysis of the TIM-HF2 trial reveals that the subgroup of HF patients with AF is highly susceptible to the benefits from RPM. This finding provides very important information for further studies and for the allocation of intensive patient care using RPM in patients with chronic HF.

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## Conflict of interest

Dr Koehler reports grants from Federal Ministry of Education and Research, during the conduct of the study; personal fees from Abbott, personal fees from Boston Scientific, personal fees from Sanofi-Aventis Deutschland GmbH, personal fees from Novartis, personal fees from Linde/Saúde, personal fees from Amgen GmbH, personal fees from Roche Pharma AG, outside the submitted work. Dr. Wachter reports grants from Deutsche Forschungsgemeinschaft, grants from Bundesministerium für Bildung und Forschung, grants from European Union, grants, personal fees, and non-financial support from Boehringer Ingelheim, personal fees and non-financial support from Novartis, personal fees and non-financial support from Bayer, personal fees and non-financial support from Berlin Chemie, personal fees and non-financial support from Medtronic, personal fees and non-financial support from Servier, personal fees and non-financial support from Bristo-Myers Squibb, personal fees and non-financial support from Daiichi Sankyo, personal fees and non-financial support from Pfizer, personal fees and non-financial support from CVRx, outside the submitted work. The remaining authors have nothing to disclose.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1.** Concomitant treatment of the patients with sinus rhythm (SR) and atrial fibrillation (AF) in the remote patient management (RPM) and usual care (UC) group at baseline (BL) versus final visit (FV).

**Table S1.** Causes of death were compared between patients in sinus rhythm and patients with atrial fibrillation.

**Table S2.** Change of the MLHFQ Questionnaire (Minnesota living with heart failure questionnaire) at 12 months. Results are shown for patients in sinus rhythm versus atrial fibrillation.

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