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ORIGINAL ARTICLE

Early detection of atrial fibrillation in patients with heart failure reduces the risk of subsequent hospitalization: a subanalysis of the randomized TIM-HF2 trial

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Aims To evaluate the rate of new-onset atrial fibrillation (AF) and the potential improved outcome in heart failure (HF) patients using non-invasive remote patient management (RPM) compared with usual care (UC).

Methods and results This analysis assessed a subgroup of 1538 patients of the TIM-HF2 trial with chronic HF, New York Heart Association Class II or III, admission to hospital for HF within 12 months before randomization, and a left ventricular ejection fraction (LVEF) of 45% or lower. Patients with AF in the baseline electrocardiogram (ECG), with an implanted cardiac device, a history of ablation therapy, and recent anticoagulation were excluded, leaving 347 patients for final analysis (RPM = 175; UC = 172). The percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause (primary endpoint of TIM-HF2), the rate of newly detected AF, and the hospitalization rate due to AF were analysed. For patients with new AF, there was a significant reduction for the primary endpoint in the RPM group [5.5%, 95% confidence interval (CI) 0–11.6 vs. UC: 14.6%, 95% CI 8.0–21.2; $P < 0.001$]. Within the first 3 months, the detection rate of new AF was significantly higher in the RPM group (5.1%) compared with UC (1.2%), $P = 0.035$. After 1 year, 23 patients (13.1%) assigned to RPM and 12 patients (7.0%) assigned to UC had newly detected AF, $P = 0.056$. Unplanned hospitalizations related to AF were significantly lower in the RPM group (2 out of 23 patients vs. UC: 10 out of 12 patients; $P < 0.001$).

Conclusion In this subgroup of HF patients in the TIM-HF2 trial, non-invasive daily ECG transmission leads to a four times higher detection rate of new AF compared with UC. This was associated with a significant reduction of days lost due to unplanned cardiovascular hospitalizations, especially hospitalizations related to AF.

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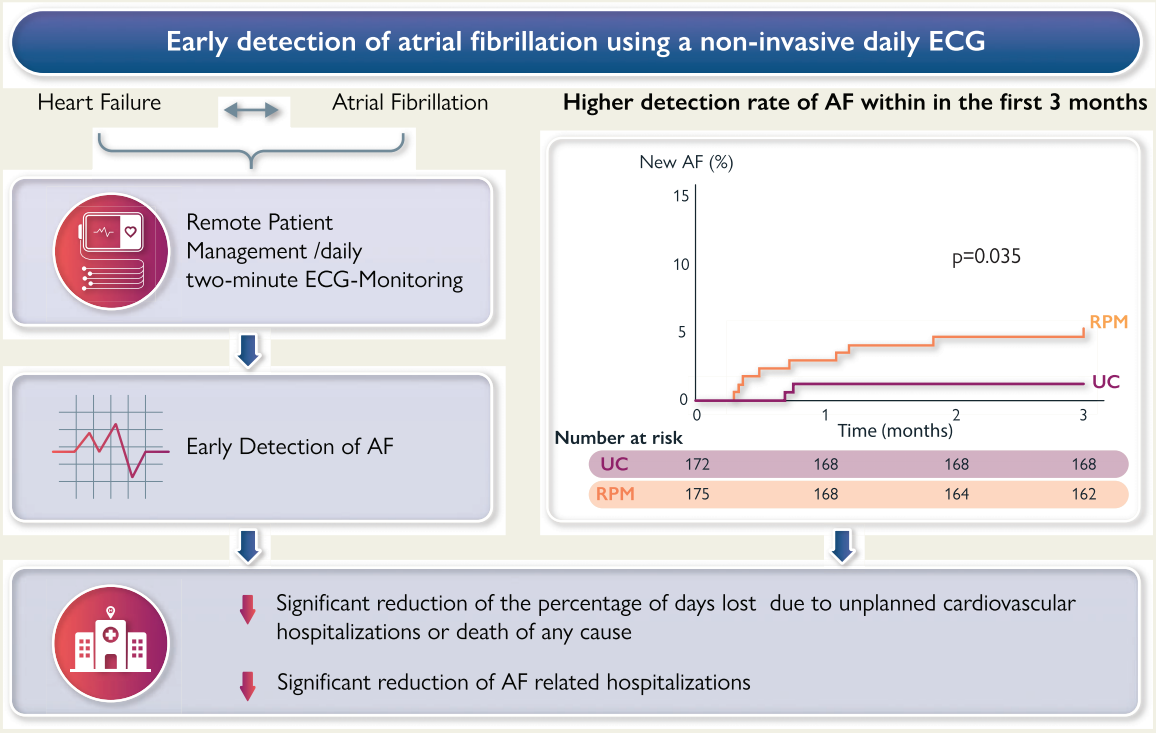
Graphical Abstract



In a subgroup-analysis of the TIM-HF2 trial, patients with heart failure (HF) and new-onset of atrial fibrillation (AF) within 1 year of follow-up lose less days for cardiovascular hospitalization or death by using non-invasive remote patient management (RPM) when compared with usual care (UC) without RPM. Daily 2 min electrocardiogram monitoring increases AF detection and is associated with a reduction in cardiovascular hospitalizations, especially unplanned hospitalizations for AF.

Keywords Remote patient management • Telemonitoring • Non-invasive • Heart failure • Atrial fibrillation • Hospitalization rate

Introduction

Recent studies suggest remote patient management (RPM) as a promising holistic ambulant care concept for symptomatic patients [New York Heart Association (NYHA) II–III] with chronic heart failure (HF) and reduced left ventricular ejection fraction (LVEF) $\leq$ 45%.[1] Patient selection for these resource-intensive concepts is important but remains challenging. Positive effects on all-cause mortality in patients with atrial fibrillation (AF) and recommended patient profiling via biomarker guidance have been reported previously.[2–4]

Atrial fibrillation and HF frequently coexist, and the prevalence of both conditions is expected to increase with the ageing of the population.[5] Multivariable analyses of two large and randomized trials, PARADIGM and ATMOSPHERE, investigated outcomes related to the type of AF in HF patients with reduced LVEF.[6] Patients with HF and paroxysmal AF were at higher risk for hospitalizations compared with persistent or permanent AF. Interestingly, patients with new-onset AF during the study period were at higher risk for all outcomes (composite of cardiovascular death or HF hospitalization, death due to worsening HF, sudden death, all-cause mortality, and stroke). Thus, HF patients with increased risk for the development of new AF seem to be a very vulnerable patient population. These patients may benefit exceedingly from close/continuous outpatient monitoring.

The detection rate of new-onset AF in HF patients with reduced LVEF using non-invasive RPM has not been reported yet. Other invasive telemedical studies observed that patients with a history of AF were more likely to benefit from telemonitoring than patients without such a history.[4]

In this *post hoc* analysis of the TIM-HF2 trial, we hypothesized that the detection rate of new-onset AF using a daily 2 min electrocardiogram (ECG), as part of non-invasive RPM, will be higher compared with usual care (UC) and an earlier AF detection may prevent unplanned hospitalizations for AF.

Methods

Study population

TIM-HF2 was a randomized controlled and parallel grouped study which was conducted in Germany and recruited patients with a history of hospitalization due to worsening HF within the last 12 months before randomization, an NYHA functional Class II or III, and an LVEF of 45% or lower (or if more than 45%, patients were being treated with oral diuretics).[1] Details of the study design, randomization, procedures, data

collection, and primary results of TIM-HF2 trial have been previously published (trial number: NCT01878630).[7] The study period was 12 months, and the patients were randomized either into the interventional group (RPM + UC) or into UC alone. Remote patient management included a 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 to the telemedical care centre (TMC), which was located at Charité—Universitätsmedizin Berlin. The TMC provided physician-led medical support for 24 h/7 days per week.

The study complied with the Declaration of Helsinki and the applicable laws and regulations. All patients provided written informed consent.

In the case report forms of the main TIM-HF2 trial, no information about known (paroxysmal, permanent, or persistent) AF, atrial flutter, or rather information about the indication for oral anticoagulation was requested at baseline. The information about AF at baseline could only be taken from the baseline resting ECGs. To ensure that patients with paroxysmal AF and indications for oral anticoagulants were not included in this analysis, we excluded all patients with oral anticoagulation at baseline to prevent selection bias. Further, all patients with an implanted cardiac device, as a correlate of continuous monitoring, were excluded. As well as all patients with a history of any type of pulmonary vein ablation (heat or cold energy) were not included. Pulmonary vein ablation is an interventional procedure to treat AF.

New detection of atrial fibrillation

One part of the RPM system was a three-channel ECG device to collect a 2 min ECG measurement (PhysioMem PM 1000 GETEMED Medizin- und Informationstechnik AG, Teltow, Germany).[7] In the main trial, the TMC provided physician-led medical support and patient management 24 h a day, Monday to Sunday, for the entire study period using the Fontane system, a CE-marked telemedical analysis software (T-Systems International GmbH, Frankfurt, Germany).[1] Algorithms in the Fontane system were programmed with cut-off limits which allowed the physicians and nurses to prioritize patients, as previously described in detail.[7]

From all selected patients assigned to RPM, all daily transmitted ECGs were screened for AF by two independent persons. Atrial fibrillation was defined according to the current guidelines: irregularly R–R intervals, absence of distinct repeating P waves, and irregular atrial activations.[8] The minimum duration of AF should last at least 30 s.[8,9] Additionally, in both groups, all medical reports from all hospital admissions were screened for a documented ECG and patients were counted when there was a documented AF which was unknown yet.

There were standard operation procedures (SOPs) implemented for the staff of the TMC including SOPs regarding anticoagulation, rhythm, and rate control management, which also included cooperation procedures with the primary treating doctor (general practitioners or cardiologists). The patients were not instructed to avoid hospitalizations and they were completely free to do a self-admission or to be admitted by the primary treating physicians at any time, no matter, what the TMC-staff recommended.

In addition, the compliance rate regarding the 2 min ECG measurement and daily transmission to the TMC was evaluated for all selected patients with sinus rhythm (SR) at baseline and assignment to RPM. Days spent in the hospital were excluded from analysis. The day after training was the possible measurement of days until the end of study minus days spent in the hospital. The results are presented in percentages.

Outcome

The primary outcome of the TIM-HF2 trial was the percentage of days lost due to unplanned cardiovascular hospitalizations or all-cause death.[1] In the TIM-HF2 trial, the reason for using the percentage of days lost was caused to the definition of the follow-up period. The follow-up period was defined as 365 days plus a 'corridor' of maximal 28 days for the final study visit.

As a result, the individual follow-up ranged between minimal 366 days and maximal 393 days. To compare the results, 'the percentage of days lost due to unplanned cardiovascular hospitalizations or all-cause death' was used as the primary endpoint of the TIM-HF2 trial. Key secondary outcomes were all-cause mortality and cardiovascular mortality.[1] In accordance with the main study, we also examined the primary and secondary endpoints for patients with newly detected AF in this subgroup analysis (RPM vs. UC). The rate of new AF was evaluated after 3 and 12 months of follow-up. Three months were chosen based on recent findings of other randomized trials which investigated the detection rate of AF in patients with stroke or patients aged 75 years or older and diagnosed with hypertension.[10,11]

In addition, all unplanned hospitalizations and all unplanned cardiovascular hospitalizations were evaluated.

Hospitalization due to atrial tachyarrhythmia

All medical reports from all hospitalized patients in both groups were screened for unplanned hospitalization due to atrial tachyarrhythmia (ATA), unplanned hospitalization with acute decompensation related to ATA, and elective hospitalization, e.g. pulmonary vein isolation ablation. A clinical endpoint committee (CEC), masked to study group assignment, adjudicated all hospital admissions during the study period using prospectively defined criteria in the CEC charter.

Statistical analyses

Statistical analysis was performed using the full analysis set of TIM-HF2 including all patients with written and signed consent. SPSS version 25 for Windows (IBM, Chicago, IL, USA) and Microsoft® Excel for Mac version 16.49 (Microsoft Corporation, Redmond, WA, USA) were used for all analyses. Baseline characteristics are presented as numbers of patients (%) for categorical variables and as mean ± standard deviation (SD) or median (25th; 75th interquartile ranges) for continuous variables, depending on the distribution. After analysis of variance, Student's *t*-test or non-parametric tests (Mann–Whitney *U*-test) were used, as appropriate. The χ^2 test or Fisher's exact test (where possible) was used for all categorical variables. Two-sided *P*-values of <0.05 were considered statistically significant.

The primary outcome was measured as described previously.[2] All-cause mortality and cardiovascular mortality curves were constructed using the Kaplan–Meier method. Differences between the curves were examined by the log-rank statistic.

Multivariable analyses were constructed using the linear regression model. Analyses considering the detection of AF were done on a time to first event basis with new AF as reference. Differences between curves were examined by the log-rank statistic. For selected comparisons between groups, the odds ratio (OR) with the 95% confidence interval (CI) are presented.

Results

Out of 1538 patients in the TIM-HF2 trial, 347 fulfilled the criteria for this subgroup analysis (see *Figure 1* for details). One hundred and seventy-five were randomized to RPM and 172 to UC. In both trial

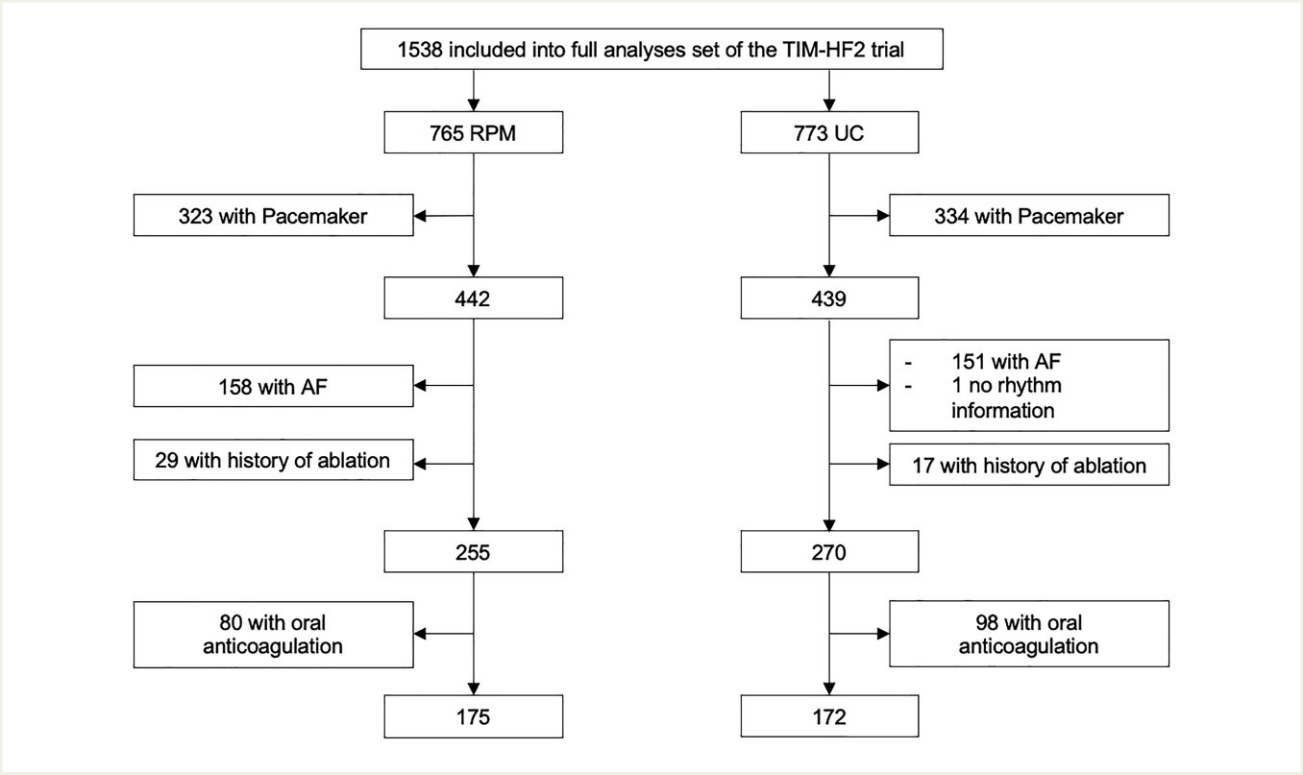


Figure 1 Patients with an implanted cardiac device, with atrial fibrillation in the baseline electrocardiogram, and with the history of ablation therapy or a recent anticoagulation were excluded. RPM, remote patient management; UC, usual care.

arms, the baseline characteristics were similar between both groups and showed a typical profile of HF patients with a high burden of comorbidities, *Table 1*.

New detection of atrial fibrillation

The detection rate of new AF within the first 3 months of the trial was significantly higher in the RPM group (RPM: 9 patients vs. UC: 2 patients; $P = 0.035$), *Figure 2A*. During 12 months of follow-up, AF was newly detected in 23 patients in the RPM group compared with 12 patients in the UC group ($P = 0.056$), *Figure 2B*. No atrial flutter was detected, neither in the daily transmitted ECGs nor in the medical reports. On average, there was a compliance rate of 95% of all patients with SR at baseline and assignment of RPM regarding the 2 min ECGs and their daily transmission to the TMC.

Independently from the randomization arm, patients with newly developed AF within 1 year of follow-up were older, had higher NT-proBNP levels, and poorer renal function at baseline (see Supplementary material online, *Table S1*). *Table 2* shows differences in baseline characteristics for patients who developed new AF compared with patients with remaining SR in the RPM and UC groups, respectively. Patients with new-onset AF in the RPM group were older and had higher NT-proBNP levels and poorer renal function at baseline, while patients with new AF in the UC group had higher NT-proBNP levels and higher blood pressure measurements. All patients with new AF had a therapeutic anticoagulation at the final study visit. Except for older age in the RPM group, there were no significant differences in the baseline characteristics of patients with new AF comparing RPM vs. UC (see Supplementary material online, *Table S2*).

Primary and secondary study outcomes

There was a significant reduction for the primary endpoint (percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause) in patients with newly detected AF and assignment to the RPM group; RPM: 5.5%, 95% CI 0–11.6 vs. UC: 14.6%, 95% CI 8.0–21.2; $P < 0.001$, *Table 3*.

Patients detected with new AF and RPM lost 7.6 days (95% CI 0.8–14.3) due to unplanned cardiovascular hospitalizations vs. 41.0 days (95% CI 18.4–64.6) in the UC group ($P < 0.001$), *Table 3*. There was also a significant reduction of days lost due to all hospitalizations for patients with newly detected AF in the RPM group compared with UC ($P < 0.001$, *Table 3*).

Figure 3 graphically shows the temporal relationship between AF detection and hospitalizations (planned and unplanned; cardiovascular and non-cardiovascular) for all patients who were newly diagnosed with AF during the study. This is only a descriptive analysis of all hospitalizations.

No significant differences were seen for the key secondary endpoints all-cause mortality and cardiovascular mortality (see Supplementary material online, *Table S3*).

Hospitalization due to tachyarrhythmia

In the UC group, 10 out of 12 patients (83%) with new detected AF had at least one hospitalization due to AF when compared with 5 out of 23 patients (22%) in the RPM group ($P < 0.001$, see Supplementary material online, *Table S4*). The other two patients in the UC group experienced ATA during the inpatient stay. For one of those, it was the first diagnosis of ATA.

Table 1 Baseline demographics and clinical characteristics of patients with sinus rhythm at baseline and without any history of atrial fibrillation

	RPM ($n = 175$)	UC ($n = 172$)	*P*-value
Age (years)	67 (11)	69 (11)	0.164
Female sex, no. (%)	60 (34)	55 (32)	0.650
Laboratory measurements			
NT-proBNP (pg/mL)	851 (300; 1912)	690 (331; 1600)	0.373
eGFR (mL/min/1.73 m^2)	73 (51; 98)	64 (46; 90)	0.223
LVEF (%) mean	43 (12)	45 (11)	0.118
<40	68 (39)	43 (25)	—
40–50	54 (31)	82 (48)	—
>50	53 (30)	47 (27)	—
Medical history			
Hypertension (mmHg)			
Systolic	131 (19)	130 (21)	0.392
Diastolic	75 (11)	75 (12)	0.558
Diabetes	69 (39)	93 (54)	0.006
Hyperlipidaemia	77 (44)	97 (56)	0.021
Coronary artery disease	89 (51)	100 (58)	0.173
Myocardial infarction	39 (22)	40 (23)	0.829
Peripheral artery disease	23 (13)	26 (15)	0.598
Valvular heart disease	83 (47)	70 (41)	0.207
COPD	32 (18)	35 (20)	0.626
Stroke	12 (7)	17 (10)	0.308
Renal insufficiency	62 (35)	82 (48)	0.021
NYHA			0.435
I	1 (1)	2 (1)	
II	110 (63)	97 (56)	
III	64 (37)	73 (42)	
IV	0 (0)	0 (0)	
Peripheral oedema	56 (32)	59 (34)	0.649
Dyspnoea on exertion	149 (85)	156 (91)	0.113
Concomitant treatment			
ACE inhibitors	99 (62)	92 (59)	0.551
AT1 inhibitors	46 (30)	63 (42)	0.038
β-Blockers	157 (91)	149 (91)	0.891
Aldosterone antagonists	91 (57)	77 (52)	0.394
Thiazides	23 (16)	29 (20)	0.358
Loop diuretics	153 (90)	147 (91)	0.572
Other diuretics	27 (18)	25 (17)	0.842
Calcium antagonists	40 (27)	50 (33)	0.268
Digitalis glycosides	3 (2)	2 (1)	1.000
Antiarrhythmic drugs	5 (3)	13 (9)	0.053

Data are presented as absolute values (per cent), mean (standard variation), or median (interquartile ranges), as appropriate. RPM, remote patient management; UC, usual care; NT-proBNP, N-terminal pro-B-type natriuretic peptide; GFR, glomerular filtration rate; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; ACE, angiotensin-converting enzyme; AT1 inhibitors, angiotensin II Type 1 receptor blocker.

In 9 out of 10 patients, the reason for hospitalization was an acute cardiac decompensation due to ATA. There was one documented elective admission for catheter ablation therapy.

In comparison, in the RPM trial arm, three of the five admissions were elective for catheter ablation therapy. Only one was acute decompensated due to ATA. One additional patient experienced ATA during the hospital stay.

Predictors for atrial fibrillation

In multivariable analysis age (OR 1.076, $P = 0.006$), NT-proBNP (OR 1.841, $P < 0.001$), and glomerular filtration rate (OR 1.017; $P = 0.011$) were independently associated with the detection of new-onset of AF throughout the 12-month study period, see Supplementary material online, *Figure S1*.

Discussion

In this *post hoc* analysis of the randomized TIM-HF2 trial, a subgroup of HF patients, without a history of AF and without implanted devices, profits by non-invasive RPM compared with UC. Patients with newly detected AF and assignment to RPM lost less percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause as opposed to patients assigned to UC. Remote patient management led to a higher and earlier atrial fibrillation detection, and this was associated with a significant reduction in AF-related hospitalizations, especially for acute cardiac decompensation due to ATA.

The reduction in days lost due to unplanned cardiovascular hospitalizations or death in the current analysis is consistent with the overall TIM-HF2 results.[1] We previously showed that patients with known AF gain augmented benefit from the telemedical intervention in the TIM-HF2 trial[2] and this was also observed in other telemedical interventions.[4] We assume that the early detection of ATA and/or bradyarrhythmia and the immediate adaption of antiarrhythmic therapy, as a part of RPM in the TIM-HF2 trial, contributed to less percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause.

Regarding different non-invasive telemonitoring technologies and studies, daily ECG monitoring remained a relatively under-investigated topic.[12,13] This is the first study reporting about the detection rate of new-onset AF in HF patients using a daily 2 min ECG. Our study demonstrated only in the first 3 months of use that RPM with daily ECG transmission can figure out nearly four times more newly detected AF compared with UC without the use of RPM. A high detection rate of new AF within the first 3 months is consistent with the results of other randomized trials evaluating screening methods for AF.[10,11] In patients with previous stroke and randomization to a prolonged 10-day Holter-ECG monitoring, 67% of AF cases in the intervention group were detected with the first 10-day Holter ECG and the participation rate during the second (after 3 months) and third (after 6 months) Holter-ECG was lower.[10] Additionally, in patients aged ≥ 75 years and diagnosed with hypertension, a 2-week continuous ECG (cECG) patch monitor at baseline showed a higher detection rate of new AF compared with 3 months.[11] Due to the small number of cases and the non-prespecified subgroup, it was not possible to evaluate if AF independently prevents HF hospitalizations or even HF worsening. But based on the recently published results and our findings, we think that there is an unmet need to investigate the possible associated clinical benefits (e.g. significant reduction in the total

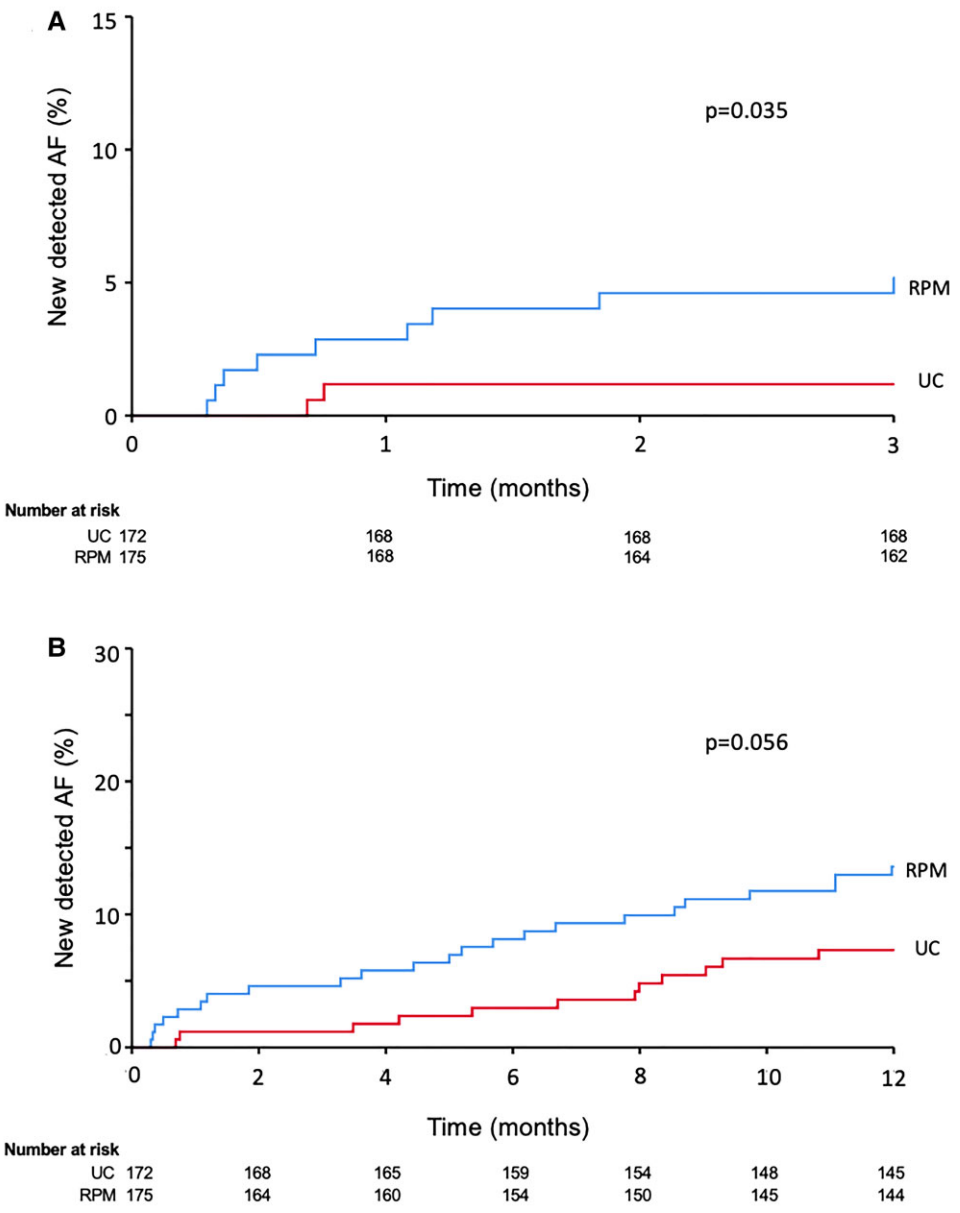


Figure 2 New detection of atrial fibrillation in the remote patient management group compared with the usual care group. (*A*) Shown for the first 3 months of the trial. (*B*) Shown for 365 days.

number of hospitalizations, worsening of HF, cost-effectiveness, or cardiovascular mortality) of early-detected AF in patients with chronic HF in a randomized controlled model.

Nevertheless, the primary target of the TIM-HF2 trial was not the detection of new-onset AF but the prevention of cardiac decompensations with unplanned hospital admissions. One reason for acute cardiac decompensations can be new-onset AF and as another thought, the AF cases revealed by RPM could have been missed or detected later using conventional diagnostics.

We presume that the most likely explanation why especially the subgroup of patients with new-onset of AF benefits from RPM is that the daily ECG transmission leads to an earlier diagnosis and treatment of AF. In contrast, the AF detection rate in our study was strikingly lower than the detection rate in the subgroup analysis of the REM-HF trial.[14] One likely explanation is that REM-HF used implantable devices with continuous monitoring, while in TIM-HF2, only 2 min ECGs per day were recorded. The earlier detection of AF was associated with a significant reduction in unplanned hospitalizations for HF and rhythm-related hospitalizations while elective hospitalizations for AF treatment (e.g. ablation therapy), mostly initiated by the TMC, were numerically increased. This could imply that daily monitoring detects atrial fibrillation early enough to prevent sudden-onset episodes of tachy- or bradyarrhythmias which potentially precipitate or accelerate hospitalizations for acute HF decompensation. Several recent studies support the concept of early AF treatment for an improvement in cardiovascular outcomes.

Table 2 Univariate analyses of the patients with newly detected atrial fibrillation compared with patients which remained in sinus rhythm

	RPM ($n = 175$)			UC ($n = 172$)		
	New AF ($n = 23$)	Remained SR ($n = 152$)	*P*-value	New AF ($n = 12$)	Remained SR ($n = 160$)	*P*-value
Age (years)	78 (68; 81)	66 (58; 75)	<0.001	69 (56; 75)	70 (62; 77)	0.431
Female sex, no. (%)	9 (39)	51 (34)	0.599	2 (17)	53 (33)	0.342
Laboratory measurements						
NT-proBNP (pg/mL)	1607 (530; 4401)	687 (292; 1676)	0.030	1553 (1243; 4099)	627 (301; 1512)	0.003
GFR (mL/min/1.73 m^2)	40 (32; 97)	74 (54; 99)	0.017	71 (47; 90)	63 (46; 90)	0.520
LVEF (%)	45 (33; 60)	40 (35; 53)	0.187	40 (34; 50)	45 (40; 55)	0.080
<40	6 (26)	62 (41)	—	6 (50)	37 (23)	—
40–50	7 (30)	47 (31)	—	6 (50)	76 (48)	—
>50	10 (44)	43 (28)	—	0 (0)	47 (29)	—
Concomitant treatment						
Hypertension (mmHg)						
Systolic	125 (120;140)	130 (119;144)	0.442	145 (125;160)	126 (110;140)	0.045
Diastolic	70 (67;80)	79 (68;80)	0.524	80 (71;90)	74(65;80)	0.048
Diabetes	9 (39)	60 (40)	0.975	8 (67)	85 (53)	0.364
Hyperlipidaemia	9 (39)	68 (45)	0.614	8 (67)	89 (56)	0.457
Coronary artery disease	12 (52)	77 (51)	0.892	8 (67)	92 (58)	0.535
Myocardial infarction	6 (26)	33 (22)	0.638	4 (33)	36 (23)	0.477
Peripheral artery disease	5 (22)	18 (12)	0.193	1 (8)	25 (16)	0.696
Valvular heart disease	12 (52)	71 (47)	0.625	4 (33)	66 (41)	0.764
COPD	3 (13)	29 (19)	0.772	2 (17)	33 (21)	1.000
Stroke	3 (13)	9 (6)	0.197	2 (17)	15 (9)	0.337
Renal insufficiency	15 (65)	47 (31)	0.001	6 (50)	76 (48)	0.867
NYHA						
I	0 (0)	1 (1)	0.227	0 (0)	2 (1)	0.059
II	11 (48)	99 (65)		3 (25)	94 (59)	
III	12 (52)	52 (34)		9 (75)	64 (40)	
IV	0 (0)	0 (0)		0 (0)	0 (0)	
Peripheral oedema	9 (39)	47 (31)	0.432	3 (25)	56 (35)	0.754
Dyspnoea on exertion	21 (91)	128 (84)	0.535	12 (100)	144 (90)	0.606

Data are presented for the RPM group and UC group, respectively. Data are presented as absolute values (per cent), mean (standard variation), or median (interquartile ranges), as appropriate. RPM, remote patient management; UC, usual care; NT-proBNP, N-terminal pro-B-type natriuretic peptide; GFR, glomerular filtration rate; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association.

As an example, the early treatment of atrial fibrillation was recently reported to reduce the adverse cardiovascular outcomes in the subgroup of HF patients in the EAST-AFNET 4 trial.[15] Our data extend these findings to an even earlier stage: early treatment is not only beneficial in those with known AF, but also those with undiagnosed AF. As a clinical consequence, HF patients should undergo regular ECG monitoring (similar to TIM-HF2) because they are prone to have undiagnosed AF.

Interestingly, HF patients were identified as the only patient population with prognostic benefits from catheter ablation.[16] That is why early diagnostic methods for the detection of atrial fibrillation are essential for the improvement of the prognosis of this patient group. Our results suggest that HF patients may be a promising patient population for the detection of new-onset of atrial fibrillation with new non-invasive diagnostic devices in future randomized trials.

Additionally, the IN-TIME trial is the only known randomized telemedical trial that reported positive effects on continuous invasive telemonitoring in patients with AF compared with SR regarding death and hospitalization rates,[4] while other invasive telemedical studies could not show any beneficial associations between the heart rhythm and the intervention.[17]

One potential speculated mechanism for the positive effects in IN-TIME was that AF was one parameter that most often led to patient contact.[4,14] This is in line with our previous findings, where patients with AF at baseline spent more time on the telephone with the TMC compared with patients in SR at baseline.[2] In contrast to our findings and the results of the IN-TIME trial, Zakeri *et al.*[14] could not show any beneficial effect on all-cause mortality for patients with known AF. But details about all-cause and cardiovascular mortality in patients with new AF are missing. For patients with new-onset AF in our *post hoc* analysis, we could not observe any significant difference in all-cause or cardiovascular mortality between the two groups. It should be highlighted that TIM-HF2 was not powered to demonstrate a survival advantage stratified by the heart rhythm.

Table 3 Presented are the percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause for patients who developed atrial fibrillation and patients which remained in sinus rhythm, compared between the randomization arms, respectively.

	New AF			Remained SR		
	RPM ($n = 23$)	UC ($n = 12$)	*P*-value	RPM ($n = 152$)	UC ($n = 160$)	*P*-value
Percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause; average (95% CI)	5.51 (0–11.58)	14.58 (7.96–21.20)	<0.001	2.70 (0.41–4.99)	4.41 (2.11–6.70)	0.073
Days lost per year[a]	20.11	53.22	—	9.86	16.10	
Days lost due to all hospitalizations (95% CI)	17.39 (6.54–28.24)	81.50 (46.40–116.56)	<0.001	6.03 (4.22–6.19)	11.49 (8.06–14.92)	0.055
Days lost due to unplanned cardiovascular hospitalizations (95% CI)	7.61 (0.83–14.34)	41.00 (18.41–63.59)	<0.001	1.79 (0.83–2.75)	3.25 (1.83–4.67)	0.105

[a]Derived from the percentage of days lost due to unplanned cardiovascular hospitalization or death of any cause: [(Percentage × 365)/100]. RPM, remote patient management; UC, usual care.

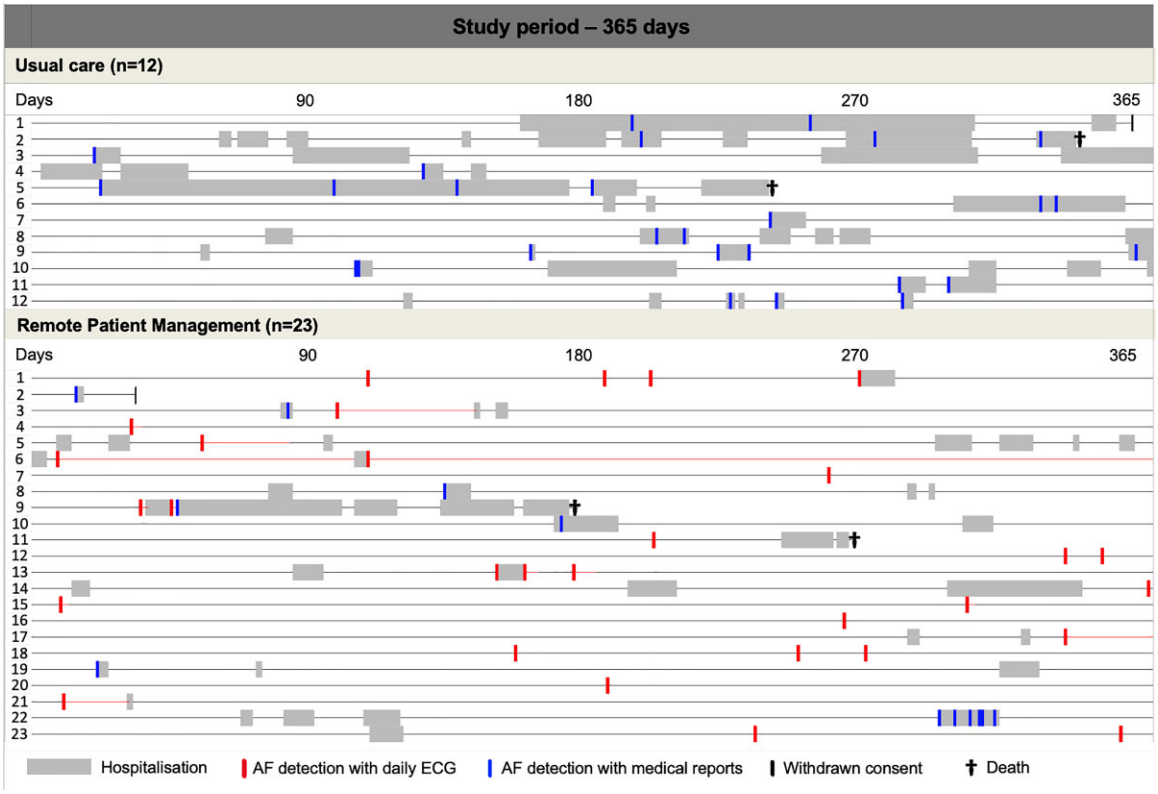


Figure 3 Presented are all patients in the interventional and usual care trial arms with newly detected atrial fibrillation during 1 year of follow-up. This central illustration gives an overview about all hospitalizations, point of death (dagger), and shows when AF was first documented either with daily electrocardiogram or with a documented ECG in the medical report.

Secondary, relating to the strong exclusion criteria we used, there remained only a small group of eligible patients for analysis.

In addition, early detection of AF allows starting, apart from early heart rate or heart rhythm control therapies, oral anticoagulation where applicable. This could be another potential mechanism to prevent AF-related hospitalizations or even stroke. In a retrospective analysis of a pooled cohort of TIM-HF and TIM-HF2, 33 ischaemic stroke-related hospitalizations were reported, with no difference between the two groups.[18] Interestingly, the rate of newly detected AF in the intervention group was also significantly higher than in the

control group (RPM: 14.1% vs. UC: 1.6%; $P < 0.001$). This is congruent with our findings. In contrast, while the summarized rate of established oral anticoagulation after new detection of AF in our analysis did not differ between the two groups, Tütüncü *et al*. report a significantly higher rate of established oral anticoagulation 12 months after randomization in the intervention group compared with the control group. Notably, there was no difference in the detection rate of new AF between study patients with stroke/TIA during the 12-month study period, compared with no stroke/TIA.

In summary, the outpatient management of HF patients, especially after discharge, is still challenging and resource-intensive.[19] Moreover, re-hospitalization rates remain high despite new therapeutic strategies and the number of repeated hospitalizations is a strong predictor of mortality.[19,20] There is still an unmet need to predict decompensation or rather detect early signs of decompensation or cardiac arrhythmia to initiate therapy immediately (e.g. up-titration of diuretics, optimize heart rate or heart rhythm control/elective ablation therapy, start anticoagulation where appropriate).[12] The feasibility of RPM in HF patients is well described but considering the latest telemedical studies and the discrepancies in their findings, characterization, and selection of the patient population that benefit the most is of great importance.[8,21–23]

There are some limitations to consider. This is a *post hoc* analysis, patients with atrial fibrillation were not a prespecified subgroup, and the study was not sufficiently powered for this sub-study. Therefore, all results are only hypothesis-generating and the findings might be similar to the main study because all patients with new AF during the follow-up period were also included in the total cohort of patients randomized to RPM. But it is of great interest to specify patients which benefit most from such cost and personnel-intensive non-invasive ambulant care programmes. The results provide important insights and should be further explored in future randomized trials. However, the sequence of earlier AF detection leading to less unplanned hospitalization for AF is biologically plausible. We did not rigorously collect information on left atrial size, function, or morphology. The clinical characteristics of patients most likely developing AF are therefore incomplete.

Due to the design of the study, we are not able to give detailed information on AF duration or AF burden. It is therefore not possible to analyse a minimal duration of AF mandating treatment from our data.

Further, patients with the assignment to UC tended to present more co-morbidities such as diabetes, hyperlipidaemia, and renal insufficiency. These differences could be explainable due to the inherent nature of the retrospective design and could potentially affect the results.

Conclusion

In our TIM-HF2-subgroup analysis, patients detected with new AF and assignment to RPM lost significantly less days due to unplanned cardiovascular hospitalization or death of any cause as opposed to patients detected with new AF and without RPM. Daily 2 min ECG monitoring may increase atrial fibrillation detection, and this could be associated with a reduction in cardiovascular hospitalizations, especially unplanned hospitalizations for atrial fibrillation.

Supplementary material

Supplementary material is available at *European Heart Journal – Digital Health*.

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Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

References

1. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan B-A, Winkler S, Vettorazzi E, Bruch L, Oeff M, Zugck C, Doerr G, Naegele H, Störk S, Butter C, Sechtem U, Angermann C, Gola G, Prondzinsky R, Edelmann F, Spethmann S, Schellong SM, Schulze PC, Bauersachs J, Wellge B, Schoebel C, Tajsic M, Dreger H, Anker SD, Stangl K. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. *Lancet* 2018;**392**:1047–1057.
2. Stegmann T, Koehler K, Wachter R, Moeller V, Zeynalova S, Koehler F, Laufs U. Heart failure patients with atrial fibrillation benefit from remote patient management: insights from the TIM-HF2 trial. *ESC Heart Fail* 2020;**5**:2516–2526.
3. Möckel M, Koehler K, Anker SD, Vollert J, Moeller V, Koehler M, Gehrig S, Wiemer JC, Haehling S, Koehler F. Biomarker guidance allows a more personalized

allocationof patients for remote patient management in heart failure: results from the TIM-HF2 trial. *Eur J Heart Fail* 2019;**21**:1445–1458.
4. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, Brachmann J, Lewalter T, Goette A, Block M, Kautzner J, Sack S, Husser D, Piorkowski C, Søgaard P. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. *Lancet* 2014;**384**:583–590.
5. Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, Ellinor PT, Cheng S, Vasan RS, Lee DS, Wang TJ, Levy D, Benjamin EJ, Ho JE. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. *Circulation* 2016;**133**:484–492.
6. Mogensen UM, Jhund PS, Abraham WT, Abraham WT, Desai AS, Dickstein K, Packer M, Rouleau JL, Solomon SD, Swedberg K, Zile MR, Køber L, McMurray JJV. Type of atrial fibrillation and outcomes in patients with heart failure and reduced ejection fraction. *J Am Coll Cardiol* 2017;**70**:2490–2500.
7. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Winkler S, Vettorazzi E, Polze A, Stangl K, Hartmann O, Marx A, Neuhaus P, Scherf M, Kirwan B-A, Anker SD. Telemedical interventional management in heart failure II (TIM-HF2), a randomised, controlled trial investigating the impact of telemedicine on unplanned cardiovascular hospitalisations and mortality in heart failure patients: study design and description of the intervention. *Eur J Heart Fail* 2018;**20**:1485–1493.
8. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau J-P, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP, Watkins CL, Kirchhof P, Kühne M, Aboyans V, Ahlsson A, Balsam P, Bauersachs J, Benussi S, Brandes A, Braunschweig F, Camm AJ, Capodanno D, Casadei B, Conen D, Crijns HJGM, Delgado V, Dobrev D, Drexel H, Eckardt L, Fitzsimons D, Folliguet T, Gale CP, Gorenek B, Haeusler KG, Heidbuchel H, Iung B, Katus HA, Kotecha D, Landmesser U, Leclercq C, Lewis BS, Mascherbauer J, Merino JL, Merkely B, Mont L, Mueller C, Nagy KV, Oldgren J, Pavlović N, Pedretti RFE, Petersen SE, Piccini JP, Popescu BA, Pürerfellner H, Richter DJ, Roffi M, Rubboli A, Scherr D, Schnabel RB, Simpson IA, Shlyakhto E, Sinner MF, Steffel J, Sousa-Uva M, Suwalski P, Svetlosak M, Touyz RM, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau J-P, Lettino M, Lip GYH, Pinto FJ, Neil Thomas G, Valgimigli M, Van Gelder IC, Watkins CL, Delassi T, Sisakian HS, Scherr D, Chasnoits A, Pauw MD, Smajić E, Shalganov T, Avraamides P, Kautzner J, Gerdes C, Alaziz AA, Kampus P, Raatikainen P, Boveda S, Papiashvili G, Eckardt L, Vassilikos V, Csanádi Z, Arnar DO, Galvin J, Barsheshet A, Caldarola P, Rakisheva A, Bytyçi I, Kerimkulova A, Kalejs O, Njeim M, Puodziukynas A, Groben L, Sammut MA, Grosu A, Boskovic A, Moustaghfir A, Groot Nd, Poposka L, Anfinsen O-G, Mitkowski PP, Cavaco DM, Siliste C, Mikhaylov EN, Bertelli L, Kojic D, Hatala R, Fras Z, Arribas F, Juhlin T, Sticherling C, Abid L, Atar I, Sychov O, Bates MGD, Zakirov NU, ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2020;**42**:373–498.
9. Charitos EI, Stierle U, Ziegler PD, Baldewig M, Robinson DR, Sievers H-H, Hanke T. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. *Circulation* 2012;**126**:806–814.
10. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D, Horn M, Weimar C, Köhrmann M, Wachter R, Rosin L, Kirchhof P. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke: a prospective multicenter cohort study. *Stroke* 2013;**44**:3357–3364.
11. Svendsen JH, Diederichsen SZ, Højberg S, Krieger DW, Graff C, Kronborg C, Olesen MS, Nielsen JB, Holst AG, Brandes A, Haugan KJ, Køber L. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *Lancet* 2021;**398**:1507–1516.
12. Faragli A, Abawi D, Quinn C, Cvetkovic M, Schlabs T, Tahirovic E, Düngen H-D, Pieske B, Kelle S, Edelmann F, Alogna A. The role of non-invasive devices for the telemonitoring of heart failure patients. *Heart Fail Rev* 2020;**26**:1063–1080.
13. Kotb A, Cameron C, Hsieh S, Wells G, Wu W-CH. Comparative effectiveness of different forms of telemedicine for individuals with heart failure (HF): a systematic review and network meta-analysis. *PLoS One* 2015;**10**:e0118681.
14. Zakeri R, Morgan JM, Phillips P, Kitt S, Ng GA, McComb JM, Williams S, Wright DJ, Gill JS, Seed A, Witte KK, Cowie MR, on behalf of the REM-HF Investigators. Impact of remote monitoring on clinical outcomes for patients with heart failure and atrial fibrillation: results from the REM-HF trial. *Eur J Heart Fail* 2020;**22**:543–553.
15. Rillig A, Magnussen C, Ozga A-K, Suling A, Brandes A, Breithardt G, Camm AJ, Crijns HJGM, Eckardt L, Elvan A, Goette A, Gulizia M, Haegeli L, Heidbuchel H, Kuck K-H, Ng A, Szumowski L, van Gelder I, Wegscheider K, Kirchhof P. Early rhythm control therapy in patients with atrial fibrillation and heart failure. *Circulation* 2021;**144**:845–858.
16. Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, Merkely B, Pokushalov E, Sanders P, Proff J, Schunkert H, Christ H, Vogt J, Bänsch D. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;**378**:417–427.
17. Morgan JM, Kitt S, Gill J, McComb JM, Ng GA, Raftery J, Roderick P, Seed A, Williams SG, Witte KK, Wright DJ, Harris S, Cowie MR. Remote management of heart failure using implantable electronic devices. *Eur Heart J* 2017;**38**:2352–2360.
18. Tütüncü S, Honold M, Koehler K, Deckwart O, Koehler F, Haeusler KG. Non-invasive telemedical care in heart failure patients and stroke: post hoc analysis of TIM-HF and TIM-HF2 trials. *ESC Heart Fail* 2020;**7**:884–891.
19. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure. *J Am Coll Cardiol* 2013;**61**:391–403.
20. Setoguchi S, Stevenson LW, Schneeweiss S. Repeated hospitalizations predict mortality in the community population with heart failure. *Am Heart J* 2007;**154**:260–266.
21. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011;**377**:658–666.
22. Böhm M, Drexler H, Oswald H, Rybak K, Bosch R, Butter C, Klein G, Gerritse B, Monteiro J, Israel C, Bimmel D, Käab S, Huegl B, Brachmann J. Fluid status telemedicine alerts for heart failure: a randomized controlled trial. *Eur Heart J* 2016;**37**:3154–3163.
23. Ong MK, Romano PS, Edgington S, Aronow HU, Auerbach AD, Black JT, De Marco T, Escarce JJ, Evangelista LS, Hanna B, Ganiats TG, Greenberg BH, Greenfield S, Kaplan SH, Kimchi A, Liu H, Lombardo D, Mangione CM, Sadeghi B, Sadeghi B, Sarrafzadeh M, Tong K, Fonarow GC, for the Better Effectiveness After Transition–Heart Failure (BEAT-HF) Research Group. Effectiveness of remote patient monitoring after discharge of hospitalized patients with heart failure: the better effectiveness after transition–heart failure (BEAT-HF) Randomized Clinical Trial. *JAMA Intern Med* 2016;**176**:310.