Mortality and morbidity 1 year after stopping a remote patient management intervention: extended follow-up results from the telemedical interventional management in patients with heart failure II (TIM-HF2) randomised trial

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Summary

Background The Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial showed that, compared with usual care, a structured remote patient management (RPM) intervention done over 12-months reduced the percentage of days lost due to unplanned cardiovascular hospitalisations and all-cause death. The aim of the study was to evaluate whether this clinical benefit seen for the RPM group during the initial 12 month follow-up of the TIM-HF2 trial would be sustained 1 year after stopping the RPM intervention.

Methods TIM-HF2 was a prospective, randomised, multicentre trial done in 43 hospitals, 60 cardiology practices, and 87 general practitioners in Germany. Patients with heart failure, New York Heart Association functional class II or III, and who had been hospitalised for heart failure within 12 months before randomisation were randomly assigned to either the RPM intervention or usual care. At the final study visit (main trial), the RPM intervention was stopped and the 1 year extended follow-up period started, which lasted 1 year. The primary outcome was percentage of days lost due to unplanned cardiovascular hospitalisations and all-cause mortality. Analyses were done using the intention-to-treat principle. This trial is registered with ClinicalTrials.gov, number NCT01878630.

Findings Between Aug 13, 2013, and May 12, 2017, 1538 patients were enrolled (765 to the remote patient management group and 773 to the usual care group) in the main trial. 671 of 765 patients in the remote patient management group and 673 of 773 in the usual care group completed the main trial and started the extended follow-up period up to 1 year later. In the extended follow-up period, the percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause mortality did not differ significantly between groups weighted mean 5·95% [95% CI 4·59–7·31] in the RPM group *vs* 6·64% [95% CI 5·19–8·08] in the usual care group [rate ratio 0·79; 95% CI 0·78–1·21]). However, when data from the main trial and the extended follow-up period were combined, the percentage of days lost due to unplanned cardiovascular hospitalisation or all-cause death was significantly less in patients allocated to the RPM group (382 [50%] of 765; weighted mean 9·28%; 95% CI 7·76–10·81) than in the UC group (398 [51%] of 773; 11·78%; 95% CI 10·08–13·49; ratio of weighted average 0·79; 95% CI 0·62–1·00; p=0·0486).

Interpretation The positive effect of our RPM intervention on morbidity and mortality over the course of the main trial was no longer observed 1 year after stopping the RPM intervention. However, because the TIM-HF2 trial was not powered to show significance during the extended follow-up period, our results are exploratory and require further research.

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Introduction

Telemedicine in heart failure is rapidly evolving.[1] As suggested in a published consensus by the Heart Failure Association of the European Society of Cardiology, regular follow-up and monitoring of clinical parameters in patients with heart failure are important to reduce morbidity and mortality.[2]

Patient education is also paramount. Telemedicine has been suggested to support patients remotely regarding both education and monitoring.[3] Effective telemonitoring programmes need access to relevant patient data in real time, appropriate staff to manage these data, and a feedback loop to patients with sufficient empowerment to understand and follow the proposed interventions.[4]

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Research in context

Evidence before this study

Over the past decade, many randomised controlled trials (RCTs) and meta-analyses have investigated the effect of remote patient management (RPM) on morbidity and mortality in patients with heart failure. Few data have been reported on how patients do in a real-world setting after participating in the respective RCT. We searched PubMed for published RCTs and meta-analyses published up to July 20, 2019. We used the search terms "telemedicine", "remote (patient) management", "telemonitoring", and "heart failure". We restricted the search to articles published in the English or German language.

We identified only one RCT, which planned to follow-up patients for an additional 6·5 years after stopping the 6-month non-invasive telemonitoring intervention. At the end of follow-up, there was no difference seen in the primary endpoint of all-cause mortality between the patients initially assigned to the RPM versus the control group.

One telemonitoring RCT based on an invasive measurement of pulmonary artery pressure investigated the long-term efficacy of this strategy. The randomised follow-up was 6 months and at the end of the trial, the haemodynamic monitoring device was activated for patients randomly assigned to the control group (initially sham). These patients and the patients initially assigned to the RPM group were then followed up for an additional (averaging) 13 months, during which the haemodynamic monitoring was switched on for both patient cohorts. During the follow-up, for patients initially assigned to the control group, heart failure hospital admissions were reduced by 48% (hazard ratio 0·52; 95% CI 0·40–0·69; p<0·0001) compared with heart failure hospital admission rates for the first 6 months in the randomised phase of the trial.

Authors of a meta-analysis done on non-invasive telemonitoring concluded that, based on their results, further research is needed to identify the optimal duration of follow-up for which non-invasive telemonitoring confers its benefits.

A Cochrane review, which included 17 non-invasive telemonitoring RCTs, reported a 30% reduction in heart failure hospitalisations and a 20% reduction in all-cause deaths during the first year under an RPM intervention. However, to date, no individual RCT investigating a non-invasive RPM intervention has showed such benefits, and thus TIM-HF2 is the first non-invasive RPM intervention trial to show these benefits.

In 2018, The Heart Failure Society of America stated that, on the basis of available evidence concerning non-invasive RPM interventions, routine use of external devices for telemonitoring is not recommended. The Heart Failure Association of the European Society of Cardiology stated that home telemonitoring using an approach that is similar to the one used in TIM-HF2 could be considered for patients with heart failure.

Added value of this study

TIM-HF2 has shown benefits on morbidity and mortality when a holistic RPM intervention combined with patient education and 24/7 TMC support with physicians and nurses is used in patients with a well-defined heart failure profile. Our trial is the first non-invasive, individual RPM intervention trial to report morbidity and mortality outcomes up to 1 year after the RPM intervention was stopped. These results might help to better guide future research on non-invasive RPM interventions, their applicability in a real-world setting, and the ideal duration of non-invasive RPM. When implementing RPM in a real-world setting of heart failure management, the results seen in the TIM-HF2 extended follow-up suggested a continuation of the RPM Intervention. Similar to invasive telemonitoring interventions, profiling of the patient population most likely to benefit from non-invasive RPM intervention in real-world setting is crucial to improve patient care.

Implications of all the available evidence

The TIM-HF2 trial is the first individual RCT to show similar benefits of an RPM intervention for morbidity and mortality as those reported in a Cochrane review, which included 17 non-invasive telemonitoring RCTs. The Heart Failure Association of the European Society of Cardiology has recommended that future research should focus on long-term real-world studies in different countries and health-care systems, rather than starting more RCT validating the fundamental concept of RPM over 6-month or 12-month follow-up. The next step for research on non-invasive RPM-interventions is to investigate the interventions applicability with respect to duration of the intervention and the management of the transmitted data in a real-world setting. This process of upscaling will certainly affect personnel and financial resources. Therefore, it is important to identify the patients with heart failure that are most likely to benefit from a non-invasive RPM intervention and to individualise the management of the transmitted data with the support of artificial intelligence. To optimise resource use in this context, RPM technology will need further improvement to manage a higher number of patients more efficiently.

Over the past decade, numerous randomised controlled trials have been done investigating the efficacy of telemonitoring interventions in heart failure.[5–13] Between these trials, the results are not comparable because of a large heterogeneity in the telemedical technology used, study designs, duration of follow-up, clinical profiles of the patients included, and study outcomes used. The published results report outcomes, observations, and findings up to the end of follow-up and the end of remote patient management (RPM) intervention; few data are available for the optimal duration of a non-invasive RPM intervention.

The Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial reported that compared with usual care, a structured RPM intervention when used in a well-defined population with heart failure over a

12-month period reduced the percentage of days lost due to unplanned cardiovascular hospitalisations and all-cause mortality.[13]

At the end of the TIM-HF2 trial, the RPM intervention was stopped and data collection for the primary and main secondary outcomes continued for an additional 12 months (ie, extended follow-up) in a real-world setting. The purpose of the prespecified extended follow-up was to evaluate, whether the benefit seen on morbidity and mortality for the RPM group during initial 12-month follow-up in the TIM-HF2 trial would be sustained over the subsequent 12 months after stopping the RPM programme. In this report, we present the morbidity-related and mortality-related outcomes up to the end of the extended follow-up period.

Methods

Study design, participants, and follow-up

The TIM-HF2 trial was a prospective, randomised, multicentre trial done in 43 hospitals, 60 cardiology practices, and 87 general practitioners in Germany. Eligible patients were randomly assigned (unmasked with randomisation concealment) to either the RPM group (n=765) or the usual care group (n=773). The study design has been previously reported.[14] Briefly, the multifaceted RPM intervention included a daily transmission of the patient's bodyweight, systolic and diastolic blood pressure, heart rate, heart rhythm analysis for 2 min, three-channel electrocardiogram, peripheral capillary oxygen saturation (SpO_2), and a self-rated health status (scale range 1–5) from the patient's home to the Telemedicine Centre (TMC) using non-invasive telemonitoring devices; creation of patient risk profiles using the baseline and follow-up visit biomarkers in addition to the daily transmitted data; patient education; and a structured collaboration between the TMC, the patient's general practitioner, and cardiologist, with respect to patient management.

Eligible patients had heart failure, were in New York Heart Association functional class II or III, had been hospitalised for heart failure within 12 months before randomisation, and had a left ventricular ejection fraction (LVEF) of either less than 45% or more than 45% if oral diuretics were prescribed. Patients with major depression were excluded. All patients who completed the main trial were seen by their cardiologist at the final study visit on day 365 (with a 28 day time window; per protocol).

The extended follow-up period started for each patient who completed the final study visit for the TIM-HF2 trial, irrespective of whether any of these patients had contributed to events for the study outcomes in the main trial, meaning that patients who died before final visit (n=142) and patients who withdrew prematurely during the main trial (n=52) did not participate in the extended follow-up period.

At the final visit, all trial-related procedures were stopped, including the RPM intervention, and patients subsequently had no further contact with the TMC. During the extended follow-up period, patients were followed up for an additional 12 months in a real-world setting; patients were no longer contacted by the TMC, and information concerning hospitalisations and mortality was obtained by the TMC from the patient's health insurance records for the occurrence of hospitalisations and for survival status.

All patients had provided written informed consent at the start of the TIM-HF2 trial for the TMC to periodically contact their health insurance company over the duration of the main trial and the extended follow-up period to obtain information concerning the occurrence of hospitalisations or information concerning survival status.

Data quality assurance

All patients included in the main trial were medically insured with either a statutory health insurance company or a private health insurance company operating in Germany.

During the main TIM-HF2 trial, the TMC did a quality control check to ascertain the completeness and accuracy of information obtained from the health insurance companies concerning the occurrence of hospitalisations; the information collected on the RPM group during daily patient contact with the TMC was compared with available information from their health insurance records.

On the average, based on the administration procedure of the hospitals billing process, the health insurance companies have on record, information concerning hospitalisations up to 2 months after the hospitalisation has taken place. For the main trial, the 1064 hospitalisations of patients in the RPM group, which were reported or identified by the TMC, were all available in the health insurance records. There was only one hospitalisation that the TMC was unaware of because it occurred during

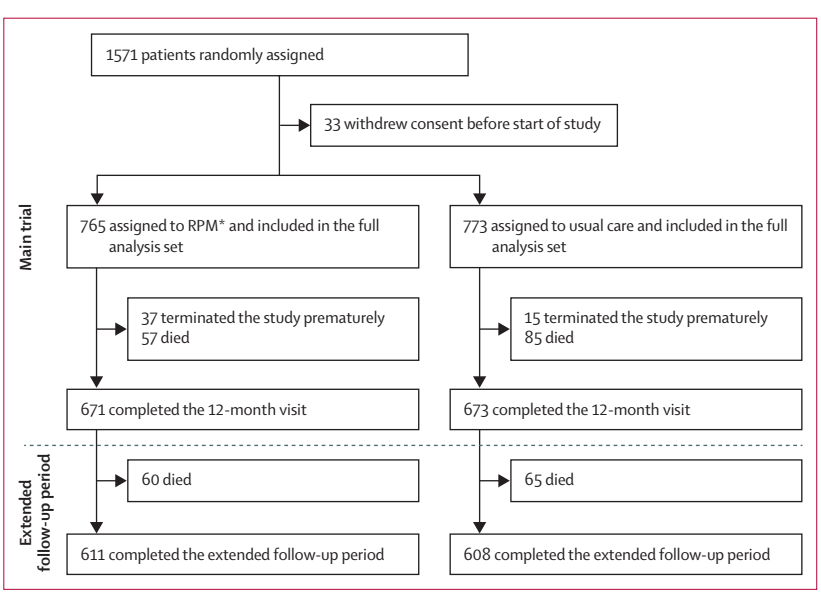

Figure 1: **Trial profile**
RPM=remote patient management. *Survival status known up to 730 days after randomisation for all patients.

a patient's holiday and did not send vital parameters on that day—the hospitalisation concerned was present in the patient's health insurance records.

We were thus confident that using the patient health insurance records to obtain information concerning hospitalisations during the extended follow-up period would be a robust method to obtain complete and accurate data concerning hospitalisations in both study groups.

Data collection during the extended follow-up

During the extended follow-up period, each patient's health insurance company was contacted at regular intervals every half year to obtain information concerning hospitalisations and deaths. For identified hospitalisations, the hospitals were contacted to obtain the corresponding discharge report. Additionally, the local residents' registration offices were accessed to obtain additional information on deaths (eg, a copy of the death certificate). This data collection procedure was approved by the German Federal Social Insurance Office and local authorities of the health insurance companies. In total, 71 German health insurance companies (20 private and 51 statutory health insurance companies) were contacted by TMC over the course of the main and extended follow-up periods. Cause of hospitalisations and deaths were adjudicated by an independent clinical endpoint committee using the same criteria as that used for the TIM-HF2 trial. The committee remained masked to the initial study group assignment.

	Remote patient management (n=671)	Usual care (n=673)
Age, years	71 (11)	71 (11)
Sex		
Female	203 (30%)	205 (30%)
Male	468 (70%)	468 (70%)
NYHA functional class		
I	97 (14%)	76 (11%)
II	347 (52%)	329 (49%)
III	214 (32%)	239 (36%)
IV	5 (1%)	8 (1%)
Not reported at final visit	8 (1%)	21 (3%)
Bodyweight, kg	88 (21)	89 (20)
Body-mass index, kg/m²	30 (6)	30 (6)
Blood pressure, mm Hg		
Systolic	126 (18)	128 (19)
Diastolic	74 (11)	75 (12)
Pulse, beats per min	71 (13)	71 (13)
Study outcomes during main trial		
Days between discharge for most recent heart failure hospital admission and final study visit		
≤30	9 (1%)	15 (2%)
31–90	19 (3%)	26 (4%)
>90	72 (11%)	93 (14%)
No heart failure hospital admission during trial	571 (85%)	539 (80%)
Percentage of days lost due to unplanned cardiovascular hospital admission during trial	2% (4)	3% (6)
Percentage of days lost due to unplanned heart failure hospital admission during trial	1% (2)	1% (3)
Number of unplanned cardiovascular hospital admissions during main trial		
0	477 (71%)	474 (70%)
1	127 (19%)	120 (18%)
2	35 (5%)	52 (8%)
3	20 (3%)	21 (3%)
4≥	12 (2%)	6 (1%)
Number of unplanned heart failure hospital admissions during main trial		
0	571 (85%)	539 (80%)
1	62 (9%)	89 (13%)
2	22 (3%)	32 (5%)
3	12 (2%)	11 (2%)
4≥	4 (1%)	2 (0%)

(Table 1 continues on next page)

Outcomes

The primary outcome for the extended follow-up period was the same as that for the main study—ie, percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause mortality. The secondary outcomes included all-cause mortality, cardiovascular mortality, and recurrent event outcomes for hospitalisations 1 year after stopping the RPM intervention. The outcomes for the extended follow-up period were compared between the randomised groups for the main trial.

Statistical analysis

The statistical software R (version 3.5.1) and Stata (version 14.2) were used for all analyses. We prespecified all data analyses in a formal statistical analysis plan, which was finalised before the database lock for the TIM-HF2 trial.

The patient clinical characteristics at the start of the extended follow-up period were summarised, by the initial randomised groups in the main TIM-HF2 trial as number (%) of patients for categorical variables. Continuous laboratory test data is summarised as median (IQR) and all other continuous data as mean (SD). All primary and secondary endpoints were compared between the initially randomised groups, thus following the intention-to-treat principle. When combining the data for the main TIM-HF2 trial and the extended follow-up periods, all patients randomised in the TIM-HF2 trial were included.

For the analysis of percentage of days lost due to unplanned cardiovascular hospitalisation and all-cause death, the proportion of follow-up time lost due to unplanned cardiovascular hospitalisation or death was defined as the number of days lost divided by the respective follow-up time. For patients who died, the number of days lost between the date of death and the date of intended end of follow-up plus the number of days spent in hospital for cardiovascular reason was counted. The two-sided permutation test p value was calculated as the fraction of permutations, which had an absolute value of the test

statistic at least as large as the observed test statistic, for which we applied a mid-P correction in case of equality. For this analysis, 2000 randomly drawn permutations were used. CIs were calculated using the method described by Garthwaite and colleagues.[15] Weighted means were calculated using the individual follow-up time as weights. For patients who died, a full weight was applied.

Survival analyses were done on a time-to-first event basis. Cumulative incidence curves for all-cause mortality were constructed according to the Kaplan-Meier method, and the differences between curves were examined by the log-rank statistic. A competing risk analysis was used for cardiovascular mortality to take into account that the event of interest could not be observed because of another previous fatal event. Cox-proportional hazards regression models were used to estimate (cause-specific) hazard ratios (HRs). The assumption of proportional hazards was checked using scaled Schoenfeld residuals. Event rates were expressed as the number of events per 100 patient-years of follow-up, taking into account the censoring of follow-up data.

The rate of recurrent cardiovascular and heart failure hospital admissions was compared using the negative binomial model with the individual follow-up time as offset. From these models, the ratios and incidences were estimated.

This trial is registered with ClinicalTrials.gov, NCT01878630.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. FK, KW, EV, and SL had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between Aug 13, 2013, and May 12, 2017, 765 patients were randomly assigned to the RPM group and 773 to the usual care group. All were included in the full analysis set in the main trial. 671 patients in the RPM group and 673 in the usual care group completed the final study visit for the main trial per protocol and continued to be followed up in the pre-specified extended follow-up period (first patient in extended follow-up Aug 7, 2014, and last patient in extended follow-up May 23, 2018; figure 1). At the start of the follow-up period, the mean age was 71 years (SD 11), and 70% were male and the clinical characteristics were well balanced between the RPM and usual care groups apart from the self-care behaviour score (ie, G9-EHFScBS-questionnaire) in which patients in the RPM group had a more favourable score than did those in the UC group (table 1). The baseline clinical characteristics that were recorded before randomisation in the main TIM-HF2 trial for the patients who continued in the extended follow-up period are shown in appendix p 2.

	Remote patient management (n=671)	Usual care (n=673)
(Continued from previous page)		
G9-EHFScBS questionnaire	14 (5)	16 (6)
Laboratory test results from final study visit		
Haemoglobin, mmol/L	8 (8–9)	8 (8–9)
Serum sodium, mmol/L	140 (138–142)	140 (138–142)
Potassium, mmol/L	4 (4–5)	4 (4–5)
Serum creatinine, µmol/L	115 (92–152)	111 (89–149)
Estimated GFR (mL/min per 1·73 m² of body surface area, Cockroft-Gault)	57 (41–83)	60 (42–85)
NT-proBNP, pg/mL	1057 (390–2180)	1071 (396–2699)
MR-proADM, nmol/L	1 (1–1)	1 (1–1)
Concomitant treatments prescribed at final study visit		
ACE inhibitors ar ARBs	523 (79%)	493 (79%)
ARN inhibitors	66 (10%)	55 (9%)
β blockers	600 (91%)	561 (90%)
Aldosterone antagonists	337 (51%)	315 (50%)
Loop diuretics	612 (93%)	568 (91%)
Thiazides	140 (21%)	139 (22%)
Other diuretics	4 (1%)	3 (0%)
Vitamin K antagonists	169 (26%)	153 (24%)
Antiplatelet therapy	38 (6%)	42 (7%)
NOACs	166 (25%)	156 (25%)
Platelet aggregation inhibitors	171 (26%)	155 (25%)
Lipid-lowering drugs	330 (50%)	309 (49%)
Insulin	141 (21%)	126 (20%)
Oral hypoglycaemic drugs	140 (21%)	129 (21%)
Ivabradine	17 (3%)	36 (6%)
Calcium antagonists	153 (23%)	136 (22%)
Nitrates	32 (5%)	39 (6%)
Digitalis glycosides	100 (15%)	104 (17%)
Antiarrhythmic drugs	81 (12%)	73 (12%)

Data are mean (SD), n (%), or median (IQR). ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. ARN=angiotensin receptor-neprilysin.G9-EHFScBS=German version of the nine-item European Heart Failure Self-care Behavior Scale. GFR=glomerular filtration rate. MR-proADM=mid-regional proadrenomedullin. NOAC=novel oral anticoagulant. NT-proBNP=N-terminal prohormone of brain natriuretic peptide. NYHA=New York Heart Association. PCI=percutaneous coronary intervention.

Table 1: **Clinical characteristics and findings at the start of the extended follow-up period**

Survival status was known for all patients of the main trial up to 730 days after randomisation (figure 1).

Over the 12-month extended follow-up period, there was no difference between the RPM and usual care groups in the percentage of days lost due to unplanned cardiovascular hospitalisation or death of any cause (rate ratio 0·97; 95% CI 0·78–1·21, p=0·82; table 2). Over this period, all-cause mortality (HR 0·92; 95% CI 0·65–1·31; p=0·66) and cardiovascular mortality per 365 days did not differ significantly between the RPM and usual care groups (table 2; figure 2; appendix p 4).

Fewer heart failure hospitalisations and cardiovascular deaths were reported in patients in the RPM group compared with patients in the UC group, but this difference was not significant (ratio 0·80; 95% CI 0·58–1·07; p=0·13; table 3). Heart failure hospitalisation and all-cause mortality

See Online for appendix

	RPM		Usual care		RPM *vs* usual care	
	Number of patients with event	Weighted average (95% CI)	Number of patients with event	Weighted average (95% CI)	Rate ratio (95% CI)	p value
Extended follow-up period						
Percentage of days lost due to unplanned cardiovascular hospital admission or death of any cause	198/671 (30%)	5·95% (4·59–7·31)	194/673 (29%)	6·64% (5·19–8·08)	0·97* (0·78–1·21)	0·82
Days lost per 365 days	..	21·7 (16·7–26·7)	..	24·2 (19·0–29·5)	..	..
All-cause mortality per 365 days	60/671 (9%)	9·38 (7·16–12·07)	65/673 (10%)	10·16 (7·84–12·95)	0·92§ (0·65–1·31)	0·655
Cardiovascular mortality per 365 days	35/671 (5%)	5·47 (3·81–7·61)	47/673 (7%)	7·35 (5·40–9·77)	0·74§ (0·48–1·15)	0·17
Main trial and extended follow-up period combined						
Percentage of days lost due to unplanned cardiovascular hospital admission or death of any cause†	382/765 (50%)	9·28% (7·76–10·81)	398/773 (51%)	11·78% (10·08–13·49)	0·79* (0·62–1·00)	0·0486
Days lost†	..	67·7 (56·6–78·9)	..	86·0 (73·6–98·5)	..	..
All-cause mortality per 730 days‡	129/765 (17%)	18·35 (15·32–21·81)	152/773 (20%)	21·82 (18·49–25·57)	0·84§ (0·66–1·06)	0·15
Cardiovascular mortality per 730 days‡	78/765 (10%)	11·10 (8·77–13·85)	102/773 (13%)	14·64 (11·94–17·77)	0·76§ (0·56–1·02)	0·07

RPM=remote patient management. *Ratio of weighted average. †For individual patient follow-up time (main trial plus 365 days of extended follow-up). ‡Up to 730 days. §Hazard ratio.

Table 2: **Primary and secondary outcomes**

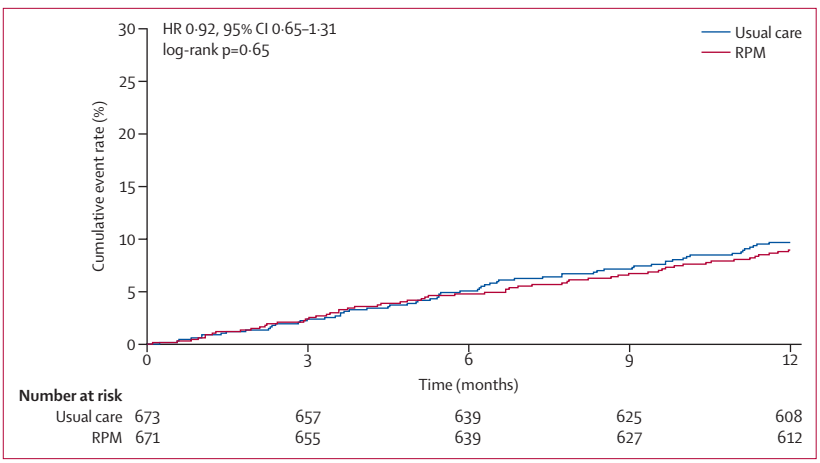

Figure 2: **Kaplan-Meier cumulative event curve for all-cause death for the extended follow-up period alone**
HR=hazard ratio. RPM=remote patient management.

did not differ significantly between the two groups (table 3). There were also fewer HF hospitalisations and all-cause deaths for patients who had been assigned to RPM compared to patients initially assigned to UC but this difference did not reach statistical significance (ratio 0·86, 95% CI 0·64–1·15, p=0·31) (table 3).

For the extended follow-up period, there were no statistically significant differences between the two randomised groups for cardiovascular hospitalisations and all-cause death and for cardiovascular hospitalisations and cardiovascular death (table 3).

When the durations of the main trial and the 12-month extended follow-up period were combined, 382 (50%) of 765 patients in the RPM group and 398 (51%) of 773 in the usual care group were hospitalised for an unplanned cardiovascular reason or died. The percentage of days lost due to unplanned cardiovascular hospitalisation or death of any cause differed significantly in patients in the RPM group compared with those in the usual care group (rate ratio 0·79; 95% CI 0·62–1·00; p=0·0486; table 2).

Survival status was available for all patients up to 730 days after randomisation in the TIM-HF2 trial. There were no significant differences in all-cause mortality per 730 days or cardiovascular mortality per 730 days up to 730 days (table 2; figure 3; appendix p 5).

Over the course of the main trial and the extended follow-up periods combined, 247 (32%) patient in the RPM group had 489 heart failure hospitalisation and cardiovascular deaths and 288 (37%) patients in the usual care group had 606 heart failure hospitalisation and cardiovascular deaths (rate ratio of 0·75, 95% CI 0·60–0·93; p=0·0089; table 3).

Over the course of the main trial and the extended follow-up periods combined, 382 (50%) patient of the RPM group had 823 cardiovascular hospital admissions and all-cause death (rate ratio 0·842, 95% CI 0·712–0·996; p=0·0453) and 366 (48%) patients in the RPM group had 766 cardiovascular hospital admission and cardiovascular deaths (rate ratio 0·839, 0·708–0·995; p=0·0436; table 3).

	RPM			Usual care			RPM *vs* usual care	
	Number of patients with event (%)	Total number of events	Incidence (95% CI)	Number of patients with event (%)	Total number of events	Incidence (95% CI)	Incidence rate ratio	p value
Extended follow-up period*								
Heart failure hospital admissions and all-cause death	148 (22%)	229	0·447 (0·363–0·552)	140 (21%)	249	0·521 (0·425–0·640)	0·858 (0·640–1·150)	0·31
Heart failure hospital admissions and cardiovascular death	131 (20%)	204	0·373 (0·299–0·464)	129 (19%)	231	0·471 (0·381–0·582)	0·791 (0·583–1·074)	0·13
Main trial and extended follow-up period combined†								
Heart failure hospital admissions and all-cause death	274 (36%)	539	0·503 (0·434–0·585)	312 (40%)	656	0·661 (0·572–0·764)	0·762 (0·619–0·938)	0·0103
Heart failure hospital admissions and cardiovascular death	247 (32%)	489	0·441 (0·377–0·516)	288 (37%)	606	0·589 (0·507–0·685)	0·749 (0·603–0·930)	0·0089
Extended follow-up period*								
Cardiovascular hospital admissions and all-cause death	198 (30%)	321	0·591 (0·498–0·701)	194 (29%)	356	0·694 (0·587–0·820)	0·851 (0·670–1·081)	0·19
Cardiovascular hospital admissions and cardiovascular death	183 (27%)	296	0·519 (0·435–0·617)	188 (28%)	338	0·642 (0·543–0·759)	0·808 (0·634–1·029)	0·0844
Main trial and extended follow-up period†								
Cardiovascular hospital admissions and all-cause death	382 (50%)	823	0·720 (0·638–0·812)	398 (51%)	922	0·855 (0·760–0·961)	0·842 (0·712–0·996)	0·0453
Cardiovascular hospital admissions and cardiovascular death	366 (48%)	773	0·656 (0·581–0·741)	381 (49%)	872	0·782 (0·694–0·880)	0·839 (0·708–0·995)	0·0436

Data are n (%), unless otherwise stated. RPM=remote patient management. *For the extended follow-up period, n=671 (639·9 patient years) in the RPM group, and n=673 (639·8 patient years) in the usual care group. †For the main trial and extended follow-up period combined, n=765 (1409·3 patient years) in the RPM group, and n=773 (1407·4 patient years) in the usual care group.

Table 3: **Results of recurrent event analysis for the extended follow-up period and for the main trial and the extended follow-up period combined**

Discussion

TIM-HF2 is the first randomised clinical trial investigating a non-invasive multiparameter telemonitoring system in patients with heart failure that showed benefits of an RPM intervention on the percentage of days lost due to unplanned cardiovascular hospitalisations and death during 1-year follow-up. The benefit in the primary endpoint seen during the main trial seemed to persist 1 year after stopping the RPM-Intervention with a borderline statistical significance, but as shown in the results of the extended follow-up period alone, there was no further gain in the difference of the primary effect size between the two study groups in the 1 year after stopping the RPM-Intervention. The results for the combined trial periods suggest that the gain in morbidity and mortality in the RPM group was not completely lost over time in the second year, which thus provides evidence of the robustness of the main trial results.

A very relevant but still unanswered question remains concerning what the ideal duration of non-invasive RPM is when used in a real-world setting and as part of standard care for patients with heart failure.[16] Because of the nature of invasive telemonitoring (ie, a permanent implant of the device), RPM is life-long or as long as the technology is switched on, and data show very promising results when this technology is used in a real-world setting.[17,18]

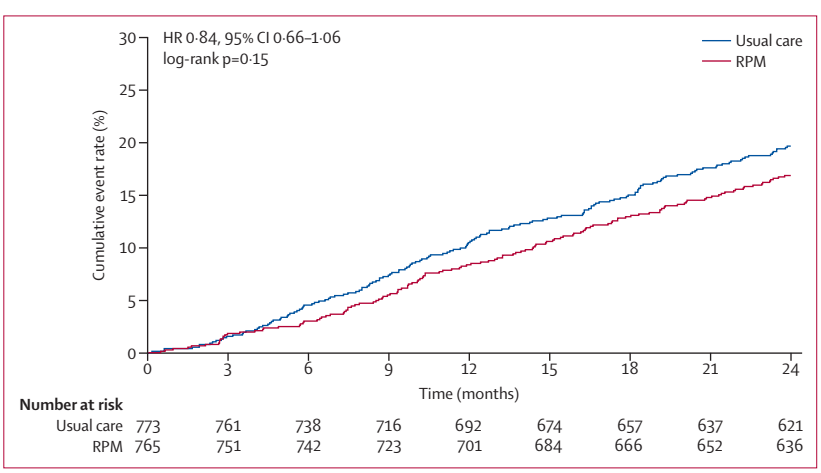

Figure 3: **Kaplan-Meier cumulative event curve for all-cause death for all patients up to 730 days after randomisation in the TIM-HF2 trial**

HR=hazard ratio. RPM=remote patient management.

For non-invasive RPM, most randomised controlled trials that reported positive outcomes, have short follow-up periods (maximally 1 year under the RPM intervention), and it is not known if the beneficial effects were sustained after stopping the RPM intervention at the end of the trials. There is only one positive trial that we are

aware of which has evaluated the effect of a 6-month non-invasive RPM intervention versus usual care on subsequent mortality.[8] The TEMA-HF1 extended follow-up trial included 141 patients who were followed up for an additional 6·5 years for mortality. The authors reported that there was no difference in all-cause mortality between the initially assigned patient groups over an extended follow-up period of 6·5 years.[19]

Another finding pertains to the patient education part of the RPM intervention. The European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure suggest that self-management is integral to achieving best patient outcomes in heart failure management to reduce mortality and improve quality of life.[20] Over the course of the TIM-HF2 trial, patient education was an important part of the RPM intervention. Patients received continuous education on the management of their disease throughout the TIM-HF2 main trial duration and were contacted once monthly–and more if needed–by the TMC nurses and TMC physicians (as appropriate). These frequent contacts might have contributed to the high adherence rates for the transfer of the data to the TMC during the main trial and perhaps contributed to the significant difference in the self-care behaviour scale, which was observed for patients assigned to the RPM group compared to UC at the starting point of the extended follow-up period (table 1). However, our results suggest that despite this intensive patient education programme, once an RPM intervention is stopped and the frequent patient contacts cease, the improved patient empowerment to manage their disease achieved during the main trial might have no impact on clinical outcomes during the extended follow-up

A longer-term non-invasive RPM duration needs to be proven to have similar outcomes as invasive telemonitoring devices, which are used for the whole lifespan of patient after implantation. For this purpose, we advocate that long-term real-world studies in different geographical and health-care settings should be done rather than initiating new RCTs that will only validate the fundamental concept of RPM.[21,22] These studies will need additional health-care resources. The identification of the patient profile most likely to benefit from an RPM intervention and an individual frequency for management of the transmitted patient data will be crucial.[23] RPM technology and future technologies could help with the process in which individualisation of patient management will prime, and data review will be presumably supported by, artificial intelligence technologies that are being developed.[24]

During the extended follow-up period, we obtained information concerning hospitalisations via the German health insurance providers. This method of collecting the outcome data could in no way have influenced the outcome of our trial as there is no incentive for physicians to hospitalise patients unless it is necessary and the insurance companies are only billed by the hospitals for hospitalisations that take place, therefore removing any form or incentive or reporting bias on the part of the insurance providers.

One of the limitations in our trial relating to the extended follow-up period is the insufficient power to detect significant differences given that for the main TIM-HF2 trial, a sample size of 1500 patients was required; however only 1344 patients started in the extended follow-up period. This kind of data collection process during the extended follow-up period is limited to the German health-care system.

In summary, our result show the positive effect of our RPM intervention on morbidity and mortality over the course of the main trial was no longer observed 1 year after stopping the RPM intervention. However, the extended follow-up period of the TIM-HF2 trial was not powered to show such differences between the initially assigned groups. Our results are thus exploratory and further long-term research is needed to determine what the ideal duration of non-invasive RPM should be when used in real-world settings to positively affect morbidity, mortality, and patient-reported outcomes. Additionally, similar to invasive telemonitoring interventions, the profiling of the patient population most likely to benefit from the non-invasive RPM intervention in a real-world setting is crucial from a patient and resource perspective.

Contributors

FK, KK, SDA, SP, OD, KS, CZ, CA, MH, and SvH contributed to the research conception and design. FK, KK, SDA, SP, OD, VM, SW, GF, JS, MK, SSt, RP, SSp, CB, HD, VS, KS, and CZ contributed to the data acquisition. FK, KK, SDA, B-AK, KW, EV, and SL contributed to the data analysis and interpretation. FK, KK, SDA, SP, OD, B-AK, KW, EV, SL, and VM contributed to the manuscript drafting. FK, KK, SDA, SP, OD, B-AK, KW, EV, SL, VM, SW, GF, JS, MK, SSt, RP, SSp, CB, CA, HD, VS, KS, CZ, MH, and SvH contributed to the critical revision of manuscript. FK obtained funding and supervised the work. KW, EV, and SL contributed to the statistical analysis.

Declaration of interests

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